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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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<p>(21) International Application Number: PCT/US92/04189 (22) International Filing Date: 19 May 1992 (19.05.92) (30) Priority data: 703,953 22 May 1991 (22.05.91) US 885,416 19 May 1992 (19.05.92) US (71) Applicant: MERCK & CO., INC. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). (72) Inventors: ASHTON, Wallace, T. ; 122 Sweet Briar Drive, Clark, NJ 07066 (US). GREENLEE, William, J. ; 115 Herrick Avenue, Teaneck, NJ 07666 (US). WU, Mu, Tsu ; 35 Lance Drive, Clark, NJ 07066 (US). DORN, Conrad, P. ; 972 Fernwood Avenue, Plainfield, NJ 07062 (US). MacCOSS, Malcolm ; 48 Rose Court, Freehold, NJ 07728 (US). MILLS, Sander, G. ; 13A Woodbridge Terrace, Woodbridge, NJ 07095 (US).</p>		<p>(74) Agent: THIES, J., Eric; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). (81) Designated States: AT (European patent), BE (European patent), CA, CH (European patent), DE (European patent), DK (European patent), ES (European patent), FR (European patent), GB (European patent), GR (European patent), IT (European patent), JP, LU (European patent), MC (European patent), NL (European patent), SE (European patent). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i></p>
<p>(54) Title: N, N-DIACYLPIPERAZINES</p> <div style="text-align: center; margin: 20px 0;"> <p>(I)</p> </div> <p>(57) Abstract</p> <p>Diacyl piperazines of general structure (I) are: angiotensin II (A-II) antagonists selective for the type 2 (AT₂) subtype useful in the treatment of cerebrovascular, cognitive, and CNS disorders; tachykinin receptor antagonists useful in the treatment of inflammatory diseases and pain or migraine; and calcium channel blockers useful in the treatment of cardiovascular conditions such as angina, hypertension or ischemia.</p>		

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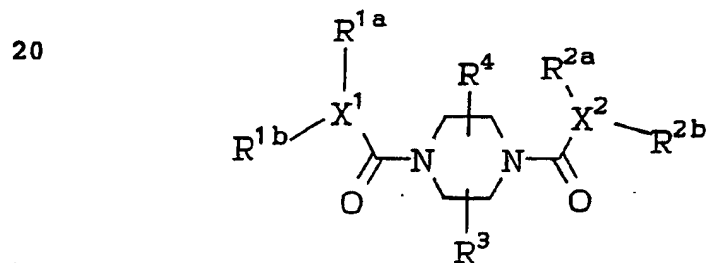
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10 TITLE OF THE INVENTION
N,N-DIACYLPIPERAZINES

SUMMARY OF THE INVENTION

15 This application is a continuation-in-part
of copending application Serial No. 07/703,953, filed
May 22, 1991.

This invention is concerned with novel
compounds represented by structural formula I:



I

30 wherein the X groups are generally N, CH or O and the
R¹ and R² groups generally are alkyl, substituted
alkyl phenyl or substituted phenyl.

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5 The invention is also concerned with pharmaceutical formulations with these novel compounds as active ingredients and the use of the novel compounds and their formulations in the treatment of certain (CNS) disorders.

10 The compounds of this invention have central nervous system (CNS) activity and are useful in the treatment of cognitive dysfunctions including Alzheimer's disease, amnesia and senile dementia. These compounds also have anxiolytic and antidepressant properties and are, therefore, useful in the relief of symptoms of anxiety and tension and in the treatment of patients with depressed or dysphoric mental states.

15 In addition, these compounds exhibit antidopaminergic properties and are thus useful to treat disorders that involve dopamine dysfunction such as schizophrenia.

20 Furthermore, these compounds are tachykinin receptor antagonists and are useful in the treatment of inflammatory diseases and pain or migraine.

25 Also, these compounds are calcium channel blockers and are useful in the treatment of cardiovascular disorders such as angina, hypertension or ischemia.

BACKGROUND OF THE INVENTION

30 It is now known that there are two subtypes of angiotensin-II (A-II) receptors, the AT₁ and AT₂ subtypes. Recent studies have shown that in rat brain, A-II receptors are primarily of the AT₂ subtype [Chang et al., Biochem. Biophys. Res.

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Commun., 171, 813 (1990)]. Agents acting as specific antagonists at these brain A-II receptors are of value in the treatment of a variety of cerebrovascular, cognitive and CNS disorders. For example, the utility of compounds having activity at the AT₂ receptor is disclosed by Bumpus, et al, Hypertension, 17, 720-721 (1991).

Receptors of the AT₂ subtype are also found in female reproductive organs of mammals, including uterus (Dudley, et al, Molecular Pharmacol., 38 370-377 (1990)) and ovaries (Pucell, et al, Endocrinology, 128, 1947-1959 (1991)). The role of angiotensin II in processes leading to ovulation has been reviewed (Andrade-Gordon, et al, Biochem. Pharmacol., 42, 715-719 (1991)).

In addition, AT₂ receptors are found in neuronal tumor cells (Speth, et al, Peptide Res., 2, 232-239 (1989)) and in transformed human neural cells (Tallant, et al, Hypertension, 17, 1135-1143 (1991)).

Some AT₂-selective A-II antagonists are known. See for example EP 245,637 and Chang et al., Mol. Pharmacol., 29, 347 (1990) which disclose compounds with structures somewhat different from those of the present application and of rather low potency. Also Whitebread et al., Biochem. Biophys. Res. Commun., 163, 284 (1989) describes a peptide with selective AT₂ antagonist properties but as with all peptides suffers rapid metabolic breakdown and lack of oral activity. Warner-Lambert PCT Patent Publication No. WO 92/05784 discloses certain AT₂-selective A-II antagonists as having a wide variety of utilities.

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Some compounds of chemical structures somewhat similar to those of the compounds of the present invention have been reported in U.S. Patents 4,089,958 and 4,138,564. However, they are reported as chemical intermediates only.

5 Some 1,4-bis(diphenylacetyl)piperazines (without substituents on the piperazine ring carbons) have been disclosed as analgesic, antipyretic, and antiinflammatory agents and CNS depressants (U.S. Patent 3,288,795). The preparation of
10 1,4-bis(diphenylcarbamoyl)piperazine has been reported [D.E. Rivett and J.F.K. Wilshire, Australian J. Chem., 19, 165 (1966)]. Unsymmetrical
15 1-acyl-4-(diphenylcarbamoyl)piperazines and 1-acyl-4-(dialkylcarbamoyl)piperazines have also been described [L. Korzycka, et al., Pol. J. Pharmacol. Pharm., 38, 545 (1986); L. Toldy, et al., Acta. Chim. Acad. Sci. Hung., 70, 101 (1971)]. All of these are unsubstituted on the piperazine ring carbons.

20 Certain 1,4-diacylpiperazine-2-carboxylates and related derivatives in which at least one of the acyl groups is substituted benzoyl have been disclosed as platelet-activating factor antagonists (U.S. Patent 4,923,870 and European Patent
25 Application EP 0,368,670). Methyl 4-(benzyloxy-carbonyl)-1-(~~tert~~-butoxycarbonyl)piperazine-2-carboxylate has been reported as an intermediate (EP 0,368,670), as has methyl 1-(benzyloxycarbonyl)-4-(~~tert~~-butoxycarbonyl)piperazine-2-carboxylate and
30 the corresponding acid [C.F. Bigge, et al., Tetrahedron Lett., 30, 5193 (1989)].

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Analgesia has historically been achieved in the central nervous system by opiates and analogs which are addictive, and peripherically by cyclooxygenase inhibitors that have gastric side effects. Substance P antagonists induce analgesia both centrally and peripherially. In addition, substance P antagonists are inhibitory of neurogenic inflammation.

The neuropeptide receptors for substance P (neurokinin-1; NK-1) are widely distributed throughout the mammalian nervous system (especially brain and spinal ganglia), the circulatory system and peripheral tissues (especially the duodenum and jejunum) and are involved in regulating a number of diverse biological processes. This includes sensory perception of olfaction, vision, audition and pain, movement control, gastric motility, vasodilation, salivation, and micturition (B. Pernow, Pharmacol. Rev., 1983, 35, 85-141).

The receptor for substance P is a member of the superfamily of G protein-coupled receptors. This superfamily is an extremely diverse group of receptors in terms of activating ligands and biological functions. In addition to the tachykinin receptors, this receptor superfamily includes the opsins, the adrenergic receptors, the muscarinic receptors, the dopamine receptors, the serotonin receptors, a thyroid-stimulating hormone receptor, a luteinizing hormone-choriogonadotropic hormone receptor, the product of the oncogene mas, the yeast mating factor receptors, a Dictyostelium cAMP receptor, and receptors for other hormones and

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neurotransmitters (see A.D. Hershey, et al., J. Biol. Chem., 1991, 226, 4366-4373).

5 Substance P (also called "SP" herein) is a naturally occurring undecapeptide belonging to the tachykinin family of peptides, the latter being so-named because of their prompt contractile action on extravascular smooth muscle tissue. The tachykinins are distinguished by a conserved carboxyl-terminal sequence Phe-X-Gly-Leu-Met-NH₂.
10 In addition to SP the known mammalian tachykinins include neurokinin A and neurokinin B. The current nomenclature designates the receptors for SP, neurokinin A, and neurokinin B as NK-1, NK-2, and NK-3, respectively.

15 More specifically, substance P is a pharmacologically-active neuropeptide that is produced in mammals and possesses a characteristic amino acid sequence that is illustrated below:

20 Arg-Pro-Lys-Pro-Gln-Gln-Phe-Phe-Gly-Leu-Met-NH₂
(Chang et al., Nature New Biol. 232, 86 (1971); D.F. Veber et al., U.S. Patent No. 4,680,283).

Neurokinin A possesses the following amino acid sequence:

His-Lys-Thr-Asp-Ser-Phe-Val-Gly-Leu-Met-NH₂.

25 Neurokinin B possesses the following amino acid sequence:

Asp-Met-His-Asp-Phe-Phe-Val-Gly-Leu-Met-NH₂.

30 Substance P acts as a vasodilator, a depressant, stimulates salivation and produces increased capillary permeability. It is also capable of producing both analgesia and hyperalgesia in

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animals, depending on dose and pain responsiveness of the animal (see R.C.A. Frederickson *et al.*, *Science*, 199, 1359 (1978); P. Oehme *et al.*, *Science*, 208, 305 (1980)) and plays a role in sensory transmission and pain perception (T.M. Jessell, *Advan. Biochem. Psychopharmacol.* 28, 189 (1981)). For example, substance P is believed *inter alia* to be involved in the neurotransmission of pain sensations [Otsuka *et al.*, "Role of Substance P as a Sensory Transmitter in Spinal Cord and Sympathetic Ganglia" in 1982 Substance P in the Nervous System, Ciba Foundation Symposium 91, 13-34 (published by Pitman) and Otsuka and Yanagisawa, "Does Substance P Act as a Pain Transmitter?" *TIPS* (Dec. 1987) 8 506-510]. In particular, substance P has been shown to be involved in the transmission of pain in migraine (see B.E.B. Sandberg *et al.*, *Journal of Medicinal Chemistry*, 25, 1009 (1982)), and in arthritis (Levine *et al.*, *Science*, (1984) 226 547-549). These peptides have also been implicated in gastrointestinal (GI) disorders and diseases of the GI tract, such as inflammatory bowel disease, ulcerative colitis and Crohn's disease, etc. (see Mantyh *et al.*, *Neuroscience*, 25 (3), 817-37 (1988) and D. Regoli in "Trends in Cluster Headache" Ed. F. Sicuteri *et al.*, Elsevier Scientific Publishers, Amsterdam, 1987, pp. 85-95).

It is also hypothesized that there is a neurogenic mechanism for arthritis in which substance P may play a role (Kidd *et al.*, "A Neurogenic Mechanism for Symmetric Arthritis" in *The Lancet*, 11 November 1989 and Gronblad *et al.*, "Neuropeptides in

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Synovium of Patients with Rheumatoid Arthritis and Osteoarthritis" in J. Rheumatol. (1988) 15(12) 1807-10). Therefore, substance P is believed to be involved in the inflammatory response in diseases such as rheumatoid arthritis and osteoarthritis (O'Byrne et al., in Arthritis and Rheumatism (1990) 33 1023-8). Other disease areas where tachykinin antagonists are believed to be useful are allergic conditions (Hamelet et al., Can. J. Pharmacol. Physiol. (1988) 66 1361-7), immunoregulation (Lotz et al., Science (1988) 241 1218-21, Kimball et al., J. Immunol. (1988) 141 (10) 3564-9 and A. Perianin, et al., Biochem. Biophys. Res. Commun. 161, 520 (1989)) vasodilation, bronchospasm, reflex or neuronal control of the viscera (Mantyh et al., PNAS (1988) 85 3235-9) and, possibly by arresting or slowing β -amyloid-mediated neurodegenerative changes (Yankner et al., Science, (1990) 250, 279-82) in senile dementia of the Alzheimer type, Alzheimer's disease and Downs Syndrome. Substance P may also play a role in demyelinating diseases such as multiple sclerosis and amyotrophic lateral sclerosis [J. Lubner-Narod et al., poster to be presented at C.I.N.P. XVIIIth Congress, 28th June-2nd July, 1992, in press].

In the recent past, some attempts have been made to provide peptide-like substances that are antagonists for substance P and other tachykinin peptides in order to more effectively treat the various disorders and diseases listed above. See for example European patent applications (EPO Publication Nos. 0,347,802, 0,401,177 and 0,412,452) which disclose various peptides as neurokinin A

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antagonists. Similarly, EPO Publication No.
0,336,230 discloses heptapeptides which are substance
P antagonists useful in the treatment of asthma.
Merck U.S. Patent No. 4,680,283 also discloses
5 peptidal analogs of substance P.

Certain inhibitors of tachykinins have been
described in U.S. Patent No. 4,501,733, by replacing
residues in substance P sequence by Trp residues.

A further class of tachykinin receptor
10 antagonists, comprising a monomeric or dimeric hexa-
or heptapeptide unit in linear or cyclic form, is
described in GB-A-2216529.

The peptide-like nature of such substances
make them too labile from a metabolic point of view
15 to serve as practical therapeutic agents in the
treatment of disease. The non-peptidic antagonists
of the present invention, on the other hand, do not
possess this drawback, as they are expected to be
more stable from a metabolic point of view than the
20 previously-discussed agents.

It is known in the art that baclofen
(β -(aminoethyl)-4-chlorobenzenepropanoic acid) in the
central nervous system effectively blocks the
excitatory activity of substance P, but because in
25 many areas the excitatory responses to other
compounds such as acetylcholine and glutamate are
inhibited as well, baclofen is not considered a
specific substance P antagonist. Pfizer WIPO patent
applications (PCT Publication Nos. WO 90/05525 and WO
30 90/05729) and publications (Science, 251, 435-437
(1991); Science, 251, 437-439 (1991)) disclose
2-arylmethyl-3-substituted amino-quinuclidine

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derivatives which are which are disclosed as being useful as substance P antagonists for treating gastrointestinal disorders, central nervous system disorders, inflammatory diseases and pain or migraine. A Glaxo European patent application (EPO Publication No. 0,360,390) discloses various spiro lactam-substituted amino acids and peptides which are antagonists or agonists of substance P. A Pfizer WIPO patent application (PCT Publication No. WO 92/06079) discloses fused-ring analogs of nitrogen-containing nonaromatic heterocycles as useful for the treatment of diseases mediated by an excess of substance P.

Calcium channel blocking agents are a known group of drugs which act to inhibit transfer of calcium ions across the plasma membrane of cells. It is known that the influx of calcium ions into certain cells in the mammalian body, including the vascular smooth muscle cells and myocardial cells, participates in the activity of such cells and that the administration of calcium channel blockers (also known as calcium antagonists or calcium entry blockers), which inhibit such influx, would suppress myocardial contractile force and rate and cause vasodilation. Calcium channel blockers delay or prevent the cardiac contracture which is believed to be caused by an accumulation of intracellular calcium under ischemic conditions. Calcium overload, during ischemia, can have a number of additional adverse effects which would further compromise the ischemic myocardium. These include less efficient use of oxygen for ATP production, activation of

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mitochondrial fatty acid oxidation, and possibly, promotion of cell necrosis. Calcium channel blockers are, therefore, useful in the treatment or prevention of a variety of diseases and disorders of the heart and vascular system, such as angina pectoris; myocardial infarction, cardiac arrhythmia, cardiac hypertrophy, coronary vasospasm, hypertension, cerebrovascular spasm and other ischemic disease. In addition, certain calcium channel blocking agents are capable of lowering elevated intraocular pressure when administered topically to the hypertensive eye in solution in a suitable ophthalmic vehicle.

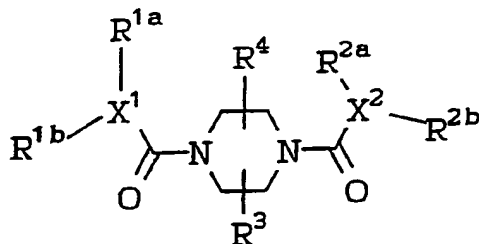
Also, certain calcium channel blockers sensitize multidrug resistant cells to certain chemotherapeutic agents and are useful in the reversal of multidrug resistance by enhancing the efficacy of various anticancer agents (J. Biol. Chem., 262 (5), 2166-2170 (1987); Scientific American, 44-51 (March 1989)). In addition, certain calcium channel blockers are suggested as having activity in blocking calcium channels in insect brain membranes and so are useful as insecticides (EMBO J., 8(8), 2365-2371 (1989)).

A number of compounds having calcium channel blocking activity are known, for example certain dihydropyridine derivatives, such as nifedipine and nicardipine, and other compounds such as verapamil, diltiazem and flunarizine.

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DETAILED DESCRIPTION OF THE INVENTION

The novel compounds of this invention are represented by structural formula I:



I

or a pharmaceutically acceptable salt thereof,
wherein:

$\text{R}^{1\text{a}}$ is

- 1) H,
- 2) C_{1-8} alkyl,
- 3) phenyl, either unsubstituted or substituted with one or two substituents selected from:
 - a) $-\text{C}_{1-4}$ alkyl,
 - b) -halo,
 - e) $-\text{OH}$,
 - d) $-\text{CF}_3$
 - e) $-\text{NH}_2$,
 - f) $-\text{NH}(\text{C}_{1-4} \text{ alkyl})$,
 - g) $-\text{N}(\text{C}_{1-4} \text{ alkyl})_2$,
 - h) $-\text{CO}_2\text{H}$,
 - i) $-\text{CO}_2(\text{C}_{1-4} \text{ alkyl})$, and
 - j) $-\text{C}_{1-4}$ alkoxy; or

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- 4) C₁₋₄ alkyl-phenyl, wherein the phenyl is either unsubstituted or substituted with one or two substituents selected from:

- 5
- a) -C₁₋₄ alkyl,
 - b) -halo,
 - e) -OH,
 - d) -CF₃
 - e) -NH₂,
 - f) -NH(C₁₋₄ alkyl),
 - 10 g) -N(C₁₋₄ alkyl)₂,
 - h) -CO₂H,
 - i) -CO₂(C₁₋₄ alkyl), and
 - j) -C₁₋₄ alkoxy;

15 R^{1b} is

- 1) R^{1a},
- 2) -C₃₋₇ cycloalkyl, or
- 3) -CH₂-R^{1a};

20 R^{2a} and R^{2b} are independently phenyl, either unsubstituted or substituted with one or two substituents selected from:

- 25
- 1) -C₁₋₄ alkoxy,
 - 2) -halo,
 - 3) -OH,
 - 4) -CF₃
 - 5) -NH₂,
 - 6) -NH(C₁₋₄ alkyl),
 - 7) -N(C₁₋₄ alkyl)₂,
 - 8) -CO₂H,
 - 30 9) -CO₂(C₁₋₄ alkyl), and

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10) -C₁₋₆ alkyl, either unsubstituted or substituted with:

- a) -halo,
- b) -OH,
- 5 c) -CF₃
- d) -NH₂,
- e) -NH(C₁₋₄ alkyl),
- f) -N(C₁₋₄ alkyl)₂,
- g) -CO₂H,
- 10 h) -CO₂(C₁₋₄ alkyl),
- i) C₁₋₄alkoxy,
- j) -S(O)_x(C₁₋₄ alkyl) wherein
x is 0, 1 or 2,
- k) -C₃₋₇ cycloalkyl;

15

and the phenyl groups of R^{2a} and R^{2b} may be joined together at the ortho carbon atoms through a carbon-carbon single bond or C₁₋₃ alkylene to form a tricyclic group with the X² to which they are attached;

20

X¹ is -N, -CH or O, and if X¹ is O, R^{1a} is absent;

X² is -N or -CH;

25

R³ is

- 1) -C₁₋₄ alkyl,
- 2) -CO₂R⁶,
- 3) -CH₂OCOR⁶,
- 4) -CH₂OH,
- 5) -CH₂OR⁵,
- 30 6) -CH₂S(O)_xR⁵,

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- 5
- 7) $-\text{CH}_2\text{OCONR}^5\text{R}^6$,
8) $-\text{CH}_2\text{CONR}^5\text{R}^6$,
9) $-\text{CONR}^5\text{R}^6$,
10) $-\text{CO}_2\text{R}^8$,
11) $-\text{CH}_2\text{CO}_2\text{R}^6$,
12) $-\text{CH}_2\text{CO}_2\text{R}^8$,
13) $-\text{CONHSO}_2\text{R}^9$,
14) $-\text{CH}_2\text{N}(\text{R}^6)\text{CONR}^5\text{R}^6$,
15) $-\text{CH}_2\text{NH}_2$,
10 16) $-\text{CH}_2\text{NH}(\text{C}_{1-4} \text{ alkyl})$, or
17) $-\text{CH}_2\text{N}(\text{C}_{1-4} \text{ alkyl})_2$; wherein

R^5 is C_{1-6} alkyl either unsubstituted or substituted with:

- 15
- 1) -halo,
2) -OH,
3) $-\text{CF}_3$,
4) $-\text{NH}_2$,
5) $-\text{NH}(\text{C}_{1-4} \text{ alkyl})$,
20 6) $-\text{N}(\text{C}_{1-4} \text{ alkyl})_2$,
7) $-\text{CO}_2\text{H}$,
8) $-\text{CO}_2(\text{C}_{1-4} \text{ alkyl})$,
9) $-\text{C}_{3-7}$ cycloalkyl, or
10) phenyl, either unsubstituted or
25 substituted with
a) $-\text{C}_{1-4} \text{ alkyl}$,
b) -halo,
c) -OH,
d) $-\text{CF}_3$,
30 e) $-\text{NH}_2$,
f) $-\text{NH}(\text{C}_{1-4} \text{ alkyl})$,
g) $-\text{N}(\text{C}_{1-4} \text{ alkyl})_2$.

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- h) $-\text{CO}_2\text{H}$, or
- i) $-\text{CO}_2(\text{C}_{1-4} \text{ alkyl})$;

R^6 is $-\text{H}$ or C_{1-4} alkyl; or

5 R^5 and R^6 can be joined together to form with the nitrogen to which they are attached $-\text{N}(\text{CH}_2\text{CH}_2)_2\text{L}$; wherein L is:

- i) a single bond,
- ii) $-\text{CH}_2-$,
- 10 iii) $-\text{O}-$,
- iv) $-\text{S}(\text{O})_p-$, or
- v) $-\text{NR}^7$;

R^7 is

- 1) $-\text{H}$,
- 15 2) $-\text{C}_{1-6}\text{alkyl}$, unsubstituted or substituted with $-\text{OH}$, $-\text{C}_{1-4}$ alkoxy or $-\text{N}(\text{C}_{1-4}\text{alkyl})_2$,
- 3) $-\text{aryl}$, or
- 4) $-\text{CH}_2\text{-aryl}$;

20

R^8 is

- 1) $-\text{H}$,
- 2) $-\text{CHOCOR}^{10}$, wherein R^{10} is
 - 25 a) $-\text{C}_{1-6}\text{alkyl}$,
 - b) $-\text{aryl}$, or
 - c) $-\text{CH}_2\text{-aryl}$,
- 3) $-\text{CH}_2\text{-aryl}$,

R^9 is

- 30 1) $-\text{aryl}$,
- 2) $-\text{heteroaryl}$,
- 3) $-\text{C}_{3-7}\text{cycloalkyl}$,

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- 4) -polyfluoro-C₁₋₄alkyl
- 5) -C₁₋₆alkyl, either unsubstituted or substituted with
- a) -aryl,
 - b) -heteroaryl,
 - c) -OH,
 - d) -SH,
 - e) -C₁₋₄alkyl,
 - f) -C₃₋₇cycloalkyl,
 - g) -C₁₋₄alkoxy,
 - h) -C₁₋₄alkylthio,
 - i) -CF₃,
 - j) -halo,
 - k) -NO₂,
 - l) -CO₂R⁶,
 - m) -N(R⁶)₂, wherein the R⁶ groups are the same or different,
 - n) -NH-aryl,
 - o) -N(aryl)₂,
 - p) -PO₃H,
 - q) -PO(OH)(OC₁₋₄alkyl) or
 - r) -N(CH₂CH₂)₂L wherein L is as defined above, and
- R⁴ is H or R³.

The term "aryl" means phenyl or naphthyl either unsubstituted or substituted with one, two or three substituents selected from the group consisting of halo, C₁₋₄-alkyl, C₁₋₄-alkoxy, NO₂, CF₃, C₁₋₄-alkylthio, OH, -N(R⁶)₂, -CO₂R⁶, C₁₋₄-perfluoroalkyl, C₃₋₆-perfluorocycloalkyl, and tetrazol-5-yl.

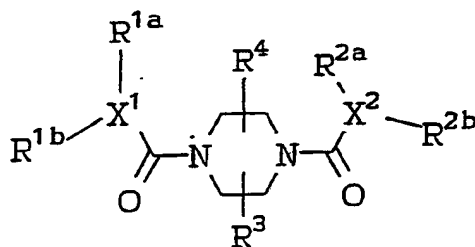
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The term "heteroaryl" means an unsubstituted, monosubstituted or disubstituted five or six membered aromatic heterocycle comprising from 1 to 3 heteroatoms selected from the group consisting of O, N and S and wherein the substituents are members selected from the group consisting of -OH, -SH, -C₁₋₄-alkyl, -C₁₋₄-alkoxy, -CF₃, halo, -NO₂, -CO₂R⁶, -N(R⁶)₂ and a fused benzo group;

The term "halo" means -Cl, -Br, -I or -F.

The term "alkyl", "alkenyl", "alkynyl" and the like include both the straight chain and branched chain species of these generic terms wherein the number of carbon atoms in the species permit. Unless otherwise noted, the specific names for these generic terms shall mean the straight chain species. For example, the term "butyl" shall mean the normal butyl substituent, n-butyl.

For the antagonism of a tachykinin receptor, preferred compounds are those represented by structural formula II:



II

or a pharmaceutically acceptable salt thereof, wherein:

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R^{1a} is

- 1) C₁₋₈ alkyl,
- 2) phenyl, either unsubstituted or substituted with one or two substituents selected from:
 - a) -C₁₋₄ alkyl,
 - b) -halo,
 - c) -OH,
 - d) -CF₃,
 - e) -NH₂,
 - f) -NH(C₁₋₄ alkyl),
 - g) -N(C₁₋₄ alkyl)₂,
 - h) -CO₂H,
 - i) -CO₂(C₁₋₄ alkyl), and
 - j) -C₁₋₄ alkoxy; or
- 3) C₁₋₄ alkyl-phenyl, wherein the phenyl is either unsubstituted or substituted with one or two substituents selected from:
 - a) -C₁₋₄ alkyl,
 - b) -halo,
 - c) -OH,
 - d) -CF₃,
 - e) -NH₂,
 - f) -NH(C₁₋₄ alkyl),
 - g) -N(C₁₋₄ alkyl)₂,
 - h) -CO₂H,
 - i) -CO₂(C₁₋₄ alkyl), and
 - j) -C₁₋₄ alkoxy;

R^{1b} is

- 1) R^{1a},
- 2) -C₃₋₇ cycloalkyl, or
- 3) -CH₂-R^{1a};

- 20 -

R^{2a} and R^{2b} are independently phenyl, either unsubstituted or substituted with one or two substituents selected from:

- 1) -C₁₋₄ alkoxy,
- 2) -halo,
- 3) -OH,
- 4) -CF₃
- 5) -NH₂,
- 6) -NH(C₁₋₄ alkyl),
- 7) -N(C₁₋₄ alkyl)₂,
- 8) -CO₂H,
- 9) -CO₂(C₁₋₄ alkyl), and
- 10) -C₁₋₆ alkyl, either unsubstituted or substituted with:
 - a) -halo,
 - b) -OH,
 - c) -CF₃
 - d) -NH₂,
 - e) -NH(C₁₋₄ alkyl),
 - f) -N(C₁₋₄ alkyl)₂,
 - g) -CO₂H,
 - h) -CO₂(C₁₋₄ alkyl),
 - i) C₁₋₄alkoxy,
 - j) -S(O)_x(C₁₋₄ alkyl) wherein x is 0, 1 or 2,
 - k) -C₃₋₇ cycloalkyl;

and the phenyl groups of R^{2a} and R^{2b} may be joined together at the ortho carbon atoms through a carbon-carbon single bond or C₁₋₃ alkylene to form a tricyclic group with the X² to which they are attached;

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X^1 is -N, -CH or O, and if X^1 is O, R^{1a} is absent;

X^2 is -N or -CH;

5 R^3 is

- 1) $-C_{1-4}$ alkyl,
- 2) $-CO_2R^6$,
- 3) $-CH_2OCOR^6$,
- 4) $-CH_2OH$,
- 10 5) $-CH_2OR^5$,
- 6) $-CH_2S(O)_xR^5$,
- 7) $-CH_2OCONR^5R^6$,
- 8) $-CH_2CONR^5R^6$,
- 9) $-CONR^5R^6$,
- 15 10) $-CH_2CO_2R^6$,
- 11) $-CO_2R^8$,
- 12) $-CONHSO_2R^9$,
- 13) $-CH_2N(R^6)CONR^5R^6$,
- 14) $-CH_2NH_2$,
- 20 15) $-CH_2NH(C_{1-4} \text{ alkyl})$, or
- 16) $-CH_2N(C_{1-4} \text{ alkyl})_2$; wherein

R^5 is C_{1-6} alkyl either unsubstituted or substituted with:

- 25 1) -halo,
- 2) -OH,
- 3) $-CF_3$,
- 4) $-NH_2$,
- 5) $-NH(C_{1-4} \text{ alkyl})$,
- 30 6) $-N(C_{1-4} \text{ alkyl})_2$,
- 7) $-CO_2H$,
- 8) $-CO_2(C_{1-4} \text{ alkyl})$,

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- 9) -C₃₋₇ cycloalkyl, or
 10) phenyl, either unsubstituted or substituted with
- a) -C₁₋₄ alkyl,
 - 5 b) -halo,
 - c) -OH,
 - d) -CF₃,
 - e) -NH₂,
 - f) -NH(C₁₋₄ alkyl),
 - 10 g) -N(C₁₋₄ alkyl)₂,
 - h) -CO₂H, or
 - i) -CO₂(C₁₋₄ alkyl);

15 R⁶ is -H or C₁₋₄ alkyl; or
 R⁵ and R⁶ can be joined together to form with the
 nitrogen to which they are attached -N(CH₂CH₂)L,
 wherein L is as defined below;

R⁷ is

- 1) -H,
- 20 2) -C₁₋₆alkyl, unsubstituted or substituted with -OH, -C₁₋₄ alkoxy or -N(C₁₋₄alkyl)₂,
- 3) -aryl, or
- 4) -CH₂-aryl;

25

R⁸ is

- 1) -H,
- 2) $\begin{array}{c} \text{R}^7 \\ | \\ -\text{CHOCOR}^{10} \end{array}$, wherein R¹⁰ is
- 30 a) -C₁₋₆alkyl,
- b) -aryl, or
- c) -CH₂-aryl,
- 3) -CH₂-aryl,

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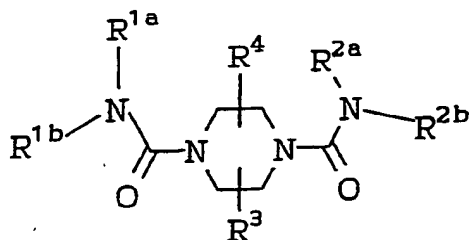
R⁹ is

- 1) -aryl,
- 2) -heteroaryl,
- 3) -C₃₋₇cycloalkyl,
- 4) -polyfluoro-C₁₋₄alkyl
- 5) -C₁₋₆alkyl, either unsubstituted or substituted with
 - a) -aryl,
 - b) -heteroaryl,
 - c) -OH
 - d) -SH
 - e) -C₁₋₄alkyl,
 - f) -C₃₋₇cycloalkyl,
 - g) -C₁₋₄alkoxy,
 - h) -C₁₋₄alkylthio,
 - i) -CF₃
 - j) -halo,
 - k) -NO₂
 - l) -CO₂R⁶
 - m) -NR⁶, wherein the R⁶ groups are the same or different,
 - n) -NH-aryl,
 - o) -N(aryl)₂,
 - p) -PO₃H,
 - q) -PO(OH)(OC₁₋₄alkyl) or
 - r) -N(CH₂CH₂)₂L wherein L is:
 - i) a single bond,
 - ii) -CH₂-,
 - iii) -O-,
 - iv) -S(O)_p -, or
 - v) -NR⁷, and

R⁴ is H or R³.

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One embodiment of the novel compounds of this invention is that wherein X^1 and X^2 are both N of structural formula:



or a pharmaceutically acceptable salt thereof.

A class of compounds within this first embodiment are those compounds wherein:

15

R^{1a} and R^{1b} are independently H, C_{1-8} alkyl or phenyl, either unsubstituted or substituted with -Cl, -Br, -I, -F, C_{1-4} alkyl, or C_{1-4} alkoxy; and R^3 is $-CO_2R^6$, or C_{1-4} alkyl; and

20

R^4 is H or R^3 .

Specific compounds within this class include:

25

1) 1-(N,N-diphenylcarbamoyl)-4-(N,N-di-n-pentylcarbamoyl)piperazine-2-carboxylic acid;

2) methyl 1-(N,N-diphenylcarbamoyl)-4-(N,N-di-n-pentylcarbamoyl)piperazine-2-carboxylate;

30

3) 1,4-bis(N,N-diphenylcarbamoyl)piperazine-2-carboxylic acid;

- 25 -

- 4) 1,4-bis(N,N-diphenylcarbamoyl)-2-methyl-
piperazine;
- 5) 1-(N,N-di-n-pentylcarbamoyl)-4-(N,N-diphenyl-
carbamoyl)piperazine-2-carboxylic acid;
- 6) 1-(N-n-pentyl-N-phenylcarbamoyl)-4-(N,N-di-
phenylcarbamoyl)piperazine-2-carboxylic acid;
- 7) 1-[N-(3-chlorophenyl)-N-phenylcarbamoyl]-4-
(N,N-di-n-pentylcarbamoyl)piperazine-2-
carboxylic acid;
- 8) 1-[N-(3-bromophenyl)-N-phenylcarbamoyl]-4-
(N,N-di-n-pentylcarbamoyl)piperazine-2-
carboxylic acid;
- 9) 1,4-bis(N,N-diphenylcarbamoyl)-trans-2,5-
dimethyl-piperazine;
- 10) 1,4-bis[N-(3-chlorophenyl)-N-phenyl-
carbamoyl]-2,5-dimethyl-piperazine, and
- 11) 1,4-bis[N-(3-chlorophenyl)-N-phenyl-
carbamoyl]-2,5-transdimethylpiperazine.

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Another class of compounds within this first embodiment are those compounds wherein:

5 R^{1a} and R^{1b} are independently H, C₁₋₈ alkyl or phenyl, either unsubstituted or substituted with -Cl, -Br, -I, -F, C₁₋₄ alkyl, or C₁₋₄ alkoxy;

R³ is -CONR⁵R⁶;

R⁴ is H or R³;

10 R⁵ is C₁₋₆ alkyl either unsubstituted or substituted with:

- 1) -halo,
- 2) -OH,
- 3) -CF₃,
- 4) -NH₂,
- 15 5) -NH(C₁₋₄ alkyl),
- 6) -N(C₁₋₄ alkyl)₂,
- 7) -CO₂H,
- 8) -CO₂(C₁₋₄ alkyl),
- 9) -C₃₋₇ cycloalkyl, or
- 20 10) phenyl, either unsubstituted or substituted with
- a) -C₁₋₄ alkyl,
- b) -halo,
- c) -OH,
- 25 d) -CF₃,
- e) -NH₂,
- f) -NH(C₁₋₄ alkyl),
- g) -N(C₁₋₄ alkyl)₂,
- h) -CO₂H, or
- 30 i) -CO₂(C₁₋₄ alkyl); and

R⁶ is -H or C₁₋₄ alkyl.

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Specific compounds within this class include:

- 1) 2-[(2-carboxyethyl)aminocarbonyl]-1-(N,N-diphenylcarbamoyl)-4-(N,N-di-n-pentylcarbamoyl)-piperazine;
5
- 2) 2-[(2-(t-butylcarboxyethyl)aminocarbonyl)-1-(N,N-diphenylcarbamoyl)-4-(N,N-di-n-pentylcarbamoyl)piperazine];
10
- 3) 2-[(3-(N,N-diethylamino)propyl)-N-methylaminocarbonyl]-1-(N,N-diphenylcarbamoyl)-4-(N,N-di-n-pentylcarbamoyl)-piperazine;
15
- 4) 2-[(2-(N,N-dimethylamino)ethyl)-N-methylaminocarbonyl]-1-(N,N-diphenylcarbamoyl)-4-(N,N-di-n-pentylcarbamoyl)-piperazine;
20
- 5) 2-[(2-(N,N-di(1-methylethyl)amino)ethyl)-aminocarbonyl]-1-(N,N-diphenylcarbamoyl)-4-(N,N-di-n-pentylcarbamoyl)piperazine;
25
- 6) 2-[(3-carboxypropyl)-N-methyl-amino-carbonyl]-1-(N,N-diphenylcarbamoyl)-4-(N,N-di-n-pentylcarbamoyl)piperazine;
30
- 7) 2-[(3-(N,N-Diethylamino)propyl)amino-carbonyl]-4-(N,N-di-n-pentylcarbamoyl)-1-(N,N-diphenylcarbamoyl)piperazine;

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- 8) 2-[(4-(N,N-Diethylamino)butyl)aminocarbonyl]-
4-(N,N-di-n-pentylcarbamoyl)-1-(N,N-diphenyl-
carbamoyl)piperazine;
- 5 9) 2-[(2-Aminoethyl)aminocarbonyl]-4-(N,N-di-
n-pentylcarbamoyl)-1-(N,N-diphenylcarbamoyl)-
piperazine;
- 10 10) 1-[N-(3-Chlorophenyl)-N-phenylcarbamoyl]-2-
[(3-(N,N-diethylamino)propyl)aminocarbonyl]-
4-(N,N-di-n-pentylcarbamoyl)piperazine;
- 15 11) 1,4-Bis[N-(3-chlorophenyl)-N-phenyl-
carbamoyl]-2-[(3-(N,N-diethylamino)propyl)-
aminocarbonyl]piperazine;
- 20 12) 1-[N-(3-Chlorophenyl)-N-phenylcarbamoyl]-2-
[(4-(N,N-diethylamino)butyl)aminocarbonyl]-
4-(N,N-di-n-pentylcarbamoyl)piperazine;
- 25 13) 2-[(3-(N,N-Diethylamino)propyl)amino-
carbonyl]-4-(N,N-di-n-pentylcarbamoyl)-1-
[N-(3-methylphenyl)-N-phenylcarbamoyl]-
piperazine;
- 30 14) 1-[N-(3-Chlorophenyl)-N-phenylcarbamoyl]-2-
[(2-(N,N-diethylamino)ethyl)aminocarbonyl]-4-
(N,N-di-n-pentylcarbamoyl)piperazine;

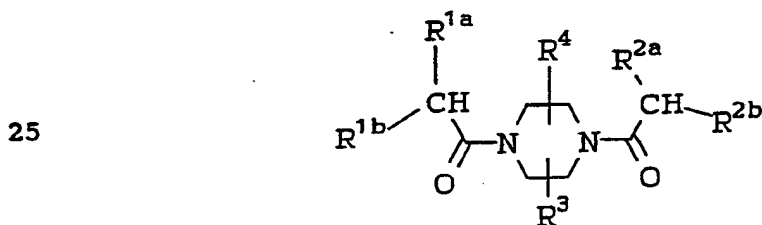
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- 15) 2-[(2-(N,N-Diethylamino)ethyl)aminocarbonyl]-
4-(N,N-di-n-pentylcarbamoyl)-1-(N,N-diphenyl-
carbamoyl)-piperazine;
- 5 16) 2-[(4-(N,N-Diethylamino)butyl)aminocarbonyl]-
1-[N-(3,5-dimethylphenyl)-N-phenylcarbamoyl]-
4-(N,N-di-n-pentylcarbamoyl)piperazine;
- 10 17) 1-[N-(3-Chlorophenyl)-N-phenylcarbamoyl]-2-
[(3-(N,N-diethylamino)propyl)aminocarbonyl]-
4-(N,N-diphenylcarbamoyl)piperazine;
- 15 18) 2-[(3-(N,N-Dimethylamino)propyl)amino-
carbonyl]-4-(N,N-di-n-pentylcarbamoyl)-1-
(N,N-diphenylcarbamoyl)piperazine;
- 20 19) 2-[(3-(N,N-Diethylamino)propyl)amino-
carbonyl]-1-[N-(3,5-dimethylphenyl)-N-
phenylcarbamoyl]-4-(N,N-di-n-pentyl-
carbamoyl)piperazine;
- 25 20) 2-[(2-(N,N-Dimethylamino)ethyl)amino-
carbonyl]-4-(N,N-di-n-pentylcarbamoyl)-1-
(N,N-diphenylcarbamoyl)piperazine;
- 30 21) 2-[(2-(N-Methylamino)ethyl-N-methyl-amino-
carbonyl]-4-(N,N-di-n-pentylcarbamoyl)-1-(N,N
-di-n-diphenylcarbamoyl)-piperazine;
- 22) 2-[(3-(N,N-diethylamino)propyl)-amino-
carbonyl]-1-[N-(3-methoxyphenyl)-N-
phenylcarbamoyl]-4-(N,N-di-n-pentyl-
carbamoyl)-piperazine;

- 23) 2-[(2-(N,N-diethylamino)ethyl)-N-(2-hydroxyethyl)aminocarbonyl]-4-(N,N-di-n-pentylcarbamoyl)-1-(N,N-diphenylcarbamoyl)-piperazine;
- 5
- 24) 2-[(3-(N,N-diethylamino)propyl)-amino-carbonyl]-1-[N-(4-hydroxyphenyl)-N-phenylcarbamoyl]-4-(N,N-di-n-pentylcarbamoyl)-piperazine, and
- 10
- 25) 2-[(2-(N,N-diethylamino)ethyl)-(N-(2-hydroxy)ethyl)aminocarbonyl]-1-[N-(3-chlorophenyl)-N-phenylcarbamoyl]-4-(N,N-di-n-pentylcarbamoyl)-piperazine.

15 Within these compounds it is especially preferred that the substituent at the 2-position be of the (S) stereochemical designation.

A second embodiment of the novel compounds of this invention is that wherein X^1 and X^2 are both CH of structural formula:



or a pharmaceutically acceptable salt thereof.

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A class of compounds within this second embodiment are those compounds wherein:

5 R^{1a} and R^{1b} are independently H, C_{1-8} alkyl or phenyl, either unsubstituted or substituted with -Cl, -Br, -I, -F, C_{1-4} alkyl, or C_{1-4} alkoxy; and

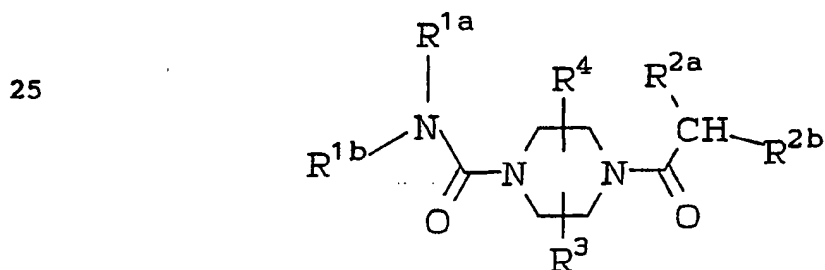
R^3 is $-CO_2R^6$, or C_{1-4} alkyl; and

10 R^4 is H or R^3 .

Specific compounds within this class include:

- 15 1) 1-diphenylacetyl-4-(3,4-dimethoxyphenyl-acetyl)-2-hydroxymethylpiperazine; and
- 2) 1-diphenylacetyl-4-(3,4-dimethoxyphenyl-acetyl)piperazine-2-carboxylic acid.

20 A third embodiment of the novel compounds of this invention is that wherein X^1 is N and X^2 is CH of structural formula:



30

or a pharmaceutically acceptable salt thereof.

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A class of compounds within this third embodiment are those compounds wherein:

5 R^{1a} and R^{1b} are independently H, C_{1-8} alkyl or phenyl, either unsubstituted or substituted with -Cl, -Br, -I, -F, C_{1-4} alkyl, or C_{1-4} alkoxy; and

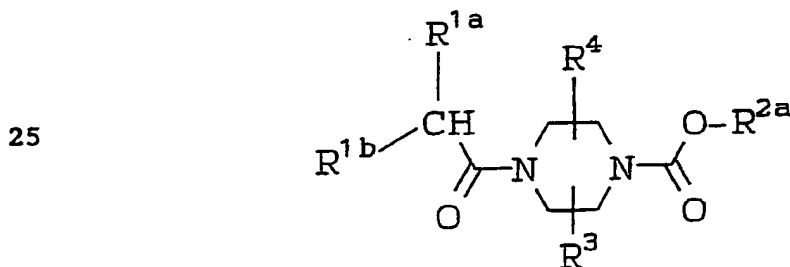
R^3 is $-CO_2R^6$, or C_{1-4} alkyl; and

10 R^4 is H or R^3 .

Specific compounds within this class include:

- 1) 1-diphenylacetyl-4-(N,N-di-n-pentyl-carbamoyl)piperazine-2-carboxylic acid; and
- 15 2) methyl 1-diphenylacetyl-4-(N,N-di-n-pentyl-carbamoyl)piperazine-2-carboxylate.

20 A fourth embodiment of the novel compounds of this invention is that wherein X^1 is CH and X^2 is O of structural formula:



30 or pharmaceutically acceptable salt thereof.

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A class of compounds within this fourth embodiment are those compounds wherein:

5 R^{1a} and R^{1b} are independently H, C_{1-8} alkyl or phenyl, either unsubstituted or substituted with -Cl, -Br, -I, -F, C_{1-4} alkyl, or C_{1-4} alkoxy; and

R^3 is $-CO_2R^6$, or C_{1-4} alkyl; and

10 R^4 is H or R^3 .

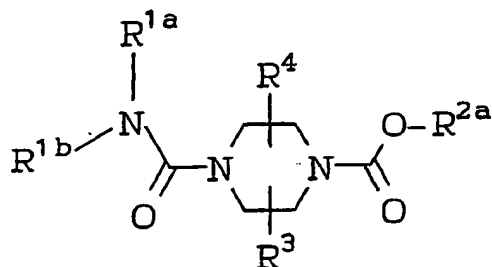
Specific compounds within this class include:

15 1) 1-diphenylacetyl-4-(benzyloxycarbonyl)-piperazine-2-carboxylic acid.

A fifth embodiment of the novel compounds of this invention is that wherein X^1 is N and X^2 is O of structural formula:

20

25



or a pharmaceutically acceptable salt thereof.

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A class of compounds within this fifth embodiment are those compounds wherein:

5 R^{1a} and R^{1b} are independently H, C_{1-8} alkyl or phenyl, either unsubstituted or substituted with -Cl, -Br, -I, -F;

10 R^{2a} is phenyl, either unsubstituted or substituted with -Cl, Br, -I, F, C_{1-4} alkyl or C_{1-4} alkoxy; and

R^3 is, $-CO_2R^6$, or C_{1-4} alkyl; and

R^4 is H or R^3 .

15 Specific compounds within this class include:

- 1) 1-(N,N-diphenylcarbamoyl)-4-(benzyloxy-carbonyl)piperazine-2-carboxylic acid;
- 20 2) 1-[N-(3-chlorophenyl)-N-phenylcarbamoyl]-4-(benzyloxy-carbonyl)piperazine-2-carboxylic acid.

25 The useful central nervous system (CNS) activities of the compounds of this invention are demonstrated and exemplified by the following assays.

COGNITIVE DYSFUNCTION ASSAY

30 The efficacy of these compounds to enhance cognitive function can be demonstrated in a rat

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passive avoidance assay in which cholinomimetics such as physostigmine and nootropic agents are known to be active. In this assay, rats are trained to inhibit their natural tendency to enter dark areas. The test apparatus used consists of two chambers, one of which is brightly illuminated and the other is dark. Rats are placed in the illuminated chamber and the elapsed time it takes for them to enter the darkened chamber is recorded. On entering the dark chamber, they receive a brief electric shock to the feet. The test animals are pretreated with 0.2 mg/kg of the muscarinic antagonist scopolamine which disrupts learning or are treated with scopolamine and the compound which is to be tested for possible reversal of the scopolamine effect. Twenty-four hours later, the rats are returned to the illuminated chamber. Upon return to the illuminated chamber, normal young rats who have been subjected to this training and who have been treated only with control vehicle take longer to re-enter the dark chamber than test animals who have been exposed to the apparatus but who have not received a shock. Rats treated with scopolamine before training do not show this hesitation when tested 24 hours later. Efficacious test compounds can overcome the disruptive effect on learning which scopolamine produces. Typically, compounds of this invention should be efficacious in this passive avoidance assay in the dose range of from about 0.1 mg/kg to about 100 mg/kg.

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ANXIOLYTIC ASSAY

The anxiolytic activity of the invention compounds can be demonstrated in a conditioned emotional response (CER) assay. Diazepam is a clinically useful anxiolytic which is active in this assay. In the CER protocol, male Sprague-Dawley rats (250-350 g) are trained to press a lever on a variable interval (VI) 60 second schedule for food reinforcement in a standard operant chamber over weekly (five days per week) training sessions. All animals then receive daily 20 minute conditioning sessions, each session partitioned into alternating 5 minute light (L) and 2 minute dark (D) periods in a fixed L1D1L2D2L3 sequence. During both periods (L or D), pressing a lever delivers food pellets on a VI 60 second schedule: in the dark (D), lever presses also elicit mild footshock (0.8 mA, 0.5 sec) on an independent shock presentation schedule of VI 20 seconds. Lever pressing is suppressed during the dark periods reflecting the formation of a conditioned emotional response (CER).

Drug testing in this paradigm is carried out under extinction conditions. During extinction, animals learn that responding for food in the dark is no longer punished by shock. Therefore, response rates gradually increase in the dark periods and animals treated with an anxiolytic drug show a more rapid increase in response rate than vehicle treated animals. Compounds of this invention should be efficacious in this test procedure in the range of from about 0.1 mg/kg to about 100 mg/kg.

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DEPRESSION ASSAY

The antidepressant activity of the compounds of this invention can be demonstrated in a tail suspension test using mice. A clinically useful antidepressant which serves as a positive control in this assay is desipramine. The method is based on the observations that a mouse suspended by the tail shows alternate periods of agitation and immobility and that antidepressants modify the balance between these two forms of behavior in favor of agitation. Periods of immobility in a 5 minute test period are recorded using a keypad linked to a microcomputer which allows the experimenter to assign to each animal an identity code and to measure latency, duration and frequency of immobile periods. Compounds of this invention should be efficacious in this test procedure in the range of from about 0.1 mg/kg to about 100 mg/kg.

SCHIZOPHRENIA ASSAY

The antidopaminergic activity of the compounds of this invention can be demonstrated in an apomorphine-induced stereotypy model. A clinically useful antipsychotic drug that is used as a positive control in this assay is haloperidol. The assay method is based upon the observation that stimulation of the dopaminergic system in rats produces stereotyped motor behavior. There is a strong correlation between the effectiveness of classical neuroleptic drugs to block apomorphine-induced stereotypy and to

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prevent schizophrenic symptoms. Stereotyped behavior induced by apomorphine, with and without pretreatment with test compounds, is recorded using a keypad linked to a microcomputer. Compounds of the invention should be efficacious in this assay in the range of from about 0.1 mg/kg to about 100 mg/kg.

The compounds of the present invention antagonize the binding of angiotensin II to AT₂ receptors and are useful in treating disorders of the CNS which are attributed to the binding of angiotensin II to AT₂ receptors. The compounds of the present invention are additionally useful in treating conditions of the female reproductive system which result from the binding of angiotensin II to AT₂ receptors in reproductive organs. The compounds of the present invention are also useful as anticancer agents for brain cancers and other cancers wherein the AT₂ receptor is prevalent.

SUBSTANCE P ANTAGONISM ASSAY

The compounds of this invention are useful for antagonizing substance P in the treatment of gastrointestinal disorders, central nervous system disorders, inflammatory diseases and pain or migraine in a mammal in need of such treatment. This activity can be demonstrated by the following assay.

A. Receptor Expression in COS

To express the cloned human neurokinin-1 receptor (NK1R) transiently in COS, the cDNA for the human NK1R was cloned into the expression vector

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pCDM9 which was derived from pCDM8 (INVITROGEN) by inserting the ampicillin resistance gene (nucleotide 1973 to 2964 from BLUESCRIPT SK+) into the Sac II site. Transfection of 20 ug of the plasmid DNA into 10 million COS cells was achieved by electroporation in 800 ul of transfection buffer (135 mM NaCl, 1.2 mM CaCl₂, 1.2 mM MgCl₂, 2.4 mM K₂HPO₄, 0.6 mM KH₂PO₄, 10 mM glucose, 10 mM HEPES pH 7.4) at 260 V and 950 uF using the IBI GENEZAPPER (IBI, New Haven, CT). The cells were incubated in 10% fetal calf serum, 2 mM glutamine, 100U/ml penicillin-streptomycin, and 90% DMEM media (GIBCO, Grand Island, NY) in 5% CO₂ at 37°C for three days before the binding assay.

15 B. Stable Expression in CHO

To establish a stable cell line expressing the cloned human NK1R, the cDNA was subcloned into the vector pRcCMV (INVITROGEN). Transfection of 20 ug of the plasmid DNA into CHO cells was achieved by electroporation in 800 ul of transfection buffer supplemented with 0.625 mg/ml Herring sperm DNA at 300 V and 950 uF using the IBI GENEZAPPER (IBI). The transfected cells were incubated in CHO media [10 % fetal calf serum, 100 U/ml pennicilin-streptomycin, 2 mM glutamine, 1/500 hypoxanthine-thymidine (ATCC), 90% IMDM media (JRH BIOSCIENCES, Lenexa, KS), 0.7 mg/ml G418 (GIBCO)] in 5% CO₂ at 37°C until colonies were visible. Each colony was separated and propagated. The cell clone with the highest number of human NK1R was selected for subsequent applications such as drug screening.

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C. Assay Protocol using COS or CHO

The binding assay of human NK1R expressed in either COS or CHO cells is based on the use of ^{125}I -substance P (^{125}I -SP, from DU PONT, Boston, MA) as a radioactively labeled ligand which competes with unlabeled substance P or any other ligand for binding to the human NK1R. Monolayer cell cultures of COS or CHO were dissociated by the non-enzymatic solution (SPECIALTY MEDIA, Lavallette, NJ) and resuspended in appropriate volume of the binding buffer (50 mM Tris pH 7.5, 5 mM MnCl_2 , 150 mM NaCl, 0.04 mg/ml bacitracin, 0.004 mg/ml leupeptin, 0.2 mg/ml BSA, 0.01 mM phosphoramidon) such that 200 μl of the cell suspension would give rise to about 10,000 cpm of specific ^{125}I -SP binding (approximately 50,000 to 200,000 cells). In the binding assay, 200 μl of cells were added to a tube containing 20 μl of 1.5 to 2.5 nM of ^{125}I -SP and 20 μl of unlabeled substance p or any other test compound. The tubes were incubated at 4°C or at room temperature for 1 hour with gentle shaking. The bound radioactivity was separated from unbound radioactivity by GF/C filter (BRANDEL, Gaithersburg, MD) which was pre-wetted with 0.1 % polyethylenimine. The filter was washed with 3 ml of wash buffer (50 mM Tris pH 7.5, 5 mM MnCl_2 , 150 mM NaCl) three times and its radioactivity was determined by gamma counter.

The activation of phospholipase C by NK1R may also be measured in CHO cells expressing the human NK1R by determining the accumulation of inositol monophosphate which is a degradation product of IP_3 . CHO cells are seeded in 12-well plate at

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250,000 cells per well. After incubating in CHO media for 4 days, cells are loaded with 0.025 uCi/ml of ^3H -myoinositol by overnight incubation. The extracellular radioactivity is removed by washing with phosphate buffered saline. LiCl is added to the well at final concentration of 0.1 mM with or without the test compound, and incubation is continued at 37°C for 15 min. Substance P is added to the well at final concentration of 0.3 nM to activate the human NK1R. After 30 min of incubation at 37°C, the media is removed and 0.1 N HCl is added. Each well is sonicated at 4°C and extracted with CHCl_3 /methanol (1:1). The aqueous phase is applied to a 1 ml Dowex AG 1X8 ion exchange column. The column is washed with 0.1 N formic acid followed by 0.025 M ammonium formate-0.1 N formic acid. The inositol monophosphate is eluted with 0.2 M ammonium formate-0.1 N formic acid and quantitated by beta counter.

As suggested by the foregoing assay, the compounds of the present invention therefore are useful in the prevention and treatment of a wide variety of clinical conditions which are characterized by the presence of an excess of tachykinin, in particular substance P, activity. These include disorders of the central nervous system such as anxiety, psychosis and schizophrenia; depression or dysthymic disorders; neurodegenerative disorders such as senile dementia of the Alzheimer type, Alzheimer's disease, AIDS related dementia and Down's syndrome; demyelinating diseases such as multiple sclerosis and amyotrophic lateral sclerosis; respiratory diseases such as bronchospasm and asthma;

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inflammatory diseases such as inflammatory bowel disease, osteoarthritis, psoriasis and rheumatoid arthritis; adverse immunological reactions such as rejection of transplanted tissues; gastrointestinal (GI) disorders and diseases of the GI tract such as disorders associated with the neuronal control of viscera such as ulcerative colitis, Crohn's disease and incontinence; disorders of blood flow caused by vasodilation; allergies such as eczema and rhinitis; chronic obstructive airways disease; hypersensitivity disorders such as poison ivy ; vasospastic diseases such as angina, migraine and Reynaud's disease; fibrosing and collagen diseases such as scleroderma and eosinophilic fascioliasis; reflex sympathetic dystrophy such as shoulder/hand syndrome; addiction disorders such as alcoholism; stress related somatic disorders; peripheral neuropathy; neuralgia; disorders related to immune enhancement or suppression such as systemic lupus erythematosus; rheumatic diseases such as fibrositis; and pain or nociception, for example, that attributable to or associated with any of the foregoing conditions or the transmission of pain in migraine. Hence, these compounds are readily adapted to therapeutic use as substance P antagonists for the control and/or treatment of any of the aforesaid clinical conditions in mammals, including humans.

As calcium channel blocking agents the compounds of the present invention are useful in the prevention of treatment of clinical conditions which benefit from inhibition of the transfer of calcium ions across the plasma membrane of cells. These

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include diseases and disorders of the heart and vascular system such as angina pectoris, myocardial infarction, cardiac arrhythmia, cardiac hypertrophy, cardiac vasospasm, hypertension, cerebrovascular spasm and other ischemic disease. Furthermore, these compounds may be capable of lowering elevated intraocular pressure when administered topically to the hypertensive eye in solution in a suitable ophthalmic vehicle. Also, these compounds may be useful in the reversal of multidrug resistance in tumor cells by enhancing the efficacy of chemotherapeutic agents. In addition, these compounds may have activity in blocking calcium channels in insect brain membranes and so may be useful as insecticides.

In the treatment of the clinical conditions noted above, the compounds of this invention may be utilized in compositions such as tablets, capsules or elixirs for oral administration, suppositories for rectal administration, sterile solutions or suspensions for parenteral or intramuscular administration, and the like. The compounds of this invention can be administered to patients (animals and human) in need of such treatment in dosages that will provide optimal pharmaceutical efficacy. Although the dose will vary from patient to patient depending upon the nature and severity of disease, the patient's weight, special diets then being followed by a patient, concurrent medication, and other factors which those skilled in the art will recognize, the dosage range will generally be about 5 to 6000 mg. per patient per day which can be administered in single or multiple

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doses. Preferably, the dosage range will be about 10 to 4000 mg. per patient per day; more preferably about 20 to 2000 mg. per patient per day.

5 In order to obtain maximal enhancement of cognitive function, the compounds of this invention may be combined with other cognition-enhancing agents. These include acetylcholinesterase inhibitors such as heptylphysostigmine and tetrahydroacridine (THA; tacrine), muscarinic agonists such as
10 oxotremorine, inhibitors of angiotensin-converting enzyme such as octylramipril, captopril, ceranapril, enalapril, lisinopril, fosinopril and zofenopril, centrally-acting calcium channel blockers and as nimodipine, and nootropic agents such as piracetam.

15 In order to achieve optimal anxiolytic activity, the compounds of this invention may be combined with other anxiolytic agents such as alprazolam, lorazepam, diazepam and buspirone.

20 In order to achieve optimal antidepressant activity, combinations of the compounds of this invention with other antidepressants are of use. These include tricyclic antidepressants such as nortriptyline, amitriptyline and trazodone, and monoamine oxidase inhibitors such as tranylcypromine.

25 In order to obtain maximal antipsychotic activity, the compounds of this invention may be combined with other antipsychotic agents such as promethazine, fluphenazine and haloperidol.

30 Several methods for preparing the compounds of this invention are illustrated in the following Schemes and Examples.

ABBREVIATIONS USED IN SCHEMES AND EXAMPLESTable 1Reagents:

5	Et ₃ N	triethylamine
	Ph ₃ P	triphenylphosphine
	TFA	trifluoroacetic acid
	NaOEt	sodium ethoxide
10	DCC	N,N'-dicyclohexylcarbodiimide
	DCU	N,N'-dicyclohexylurea
	CDI	1,1'-carbonyldiimidazole
	MCPBA	m-chloroperbenzoic acid
	DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
15	Cbz-Cl	benzyl chloroformate
	iPr ₂ NEt or DIEA	N,N-diisopropylethylamine
	NHS	N-hydroxysuccinimide
	DIBAL	diisobutylaluminum hydride
	Me ₂ SO ₄	dimethyl sulfate
20	HOBt	1-hydroxybenzotriazole hydrate
	EDAC	1-ethyl-3-(3-dimethylaminopropyl)carbo- diimide hydrochloride

Solvents:

25	DMF	dimethylformamide
	THF	tetrahydrofuran
	MeOH	methanol
	EtOH	ethanol
	AmOH	n-amyl alcohol
30	AcOH	acetic acid
	MeCN	acetonitrile
	DMSO	dimethylsulfoxide

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Others:

	Ph	phenyl
	Ar	aryl
	Me	methyl
5	Et	ethyl
	iPr	isopropyl
	Am	n-amyl
	Cbz	carbobenzyloxy (benzyloxycarbonyl)
	Boc	<u>tert</u> -butoxycarbonyl
10	PTC	phase transfer catalyst
	cat.	catalytic
	FAB-MS	fast atom bombardment mass spectrometry

For the synthesis of compounds of formula I,
15 the central piperazine nucleus may be constructed by
various methods. One such useful method, shown in
Scheme 1, entails catalytic hydrogenation of a
substituted pyrazine 1 to give the piperazine 2 [E.
Felder, et al., Helv. Chim. Acta, 43, 888 (1960)].
20 This is typically accomplished by use of palladium on
carbon as the catalyst, in a solvent such as ethanol
or water, at a temperature of 20-50°C.

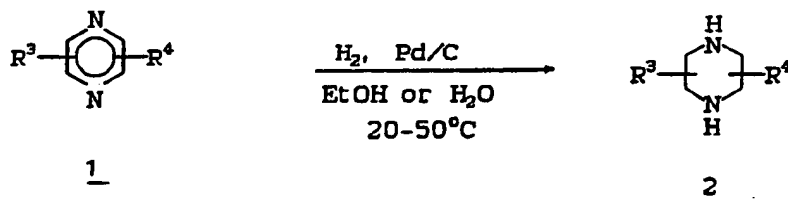
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SCHEME 1

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Another method (Scheme 2) involves reaction of a protected diamine 3 with a dibromo compound 4 in the presence of base at elevated temperature to give the bis-protected piperazine 5, which yields 2 upon deprotection. This method has been particularly useful in cases where 4 is a 2,3-dibromo ester. In the variation used by Piper, et al. [J.R.Piper, L.M. Rose, and T.P. Johnston, J. Org. Chem., 37, 4476 (1972)], the protecting group P is p-toluenesulfonyl, and the disodium salt of 3 is heated with 4 (R=CO₂Et) in DMF at up to about 100-110°C to form the piperazine 5. The p-toluenesulfonyl protecting groups can be removed (along with simultaneous ester

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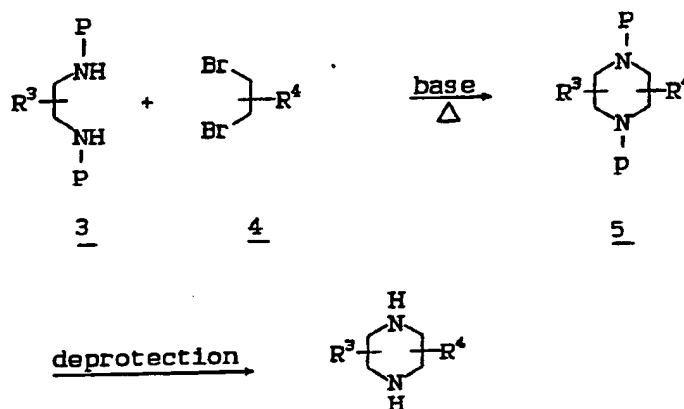
hydrolysis) by heating 5 at reflux in 48% HBr [F.L. Bach, Jr., *et al.*, *J. Am. Chem. Soc.*, 77, 6049 (1955). In another variation [E. Jucker and E. Rissi, *Helv. Chim. Acta*, 45, 2383 (1962)], the protecting group P is benzyl, and heating 3 with 4 ($R^4=CO_2Et$) in benzene yields 5. In this case deprotection is achieved (without ester hydrolysis) by palladium-catalyzed hydrogenation in acetic acid.

SCHEME 2

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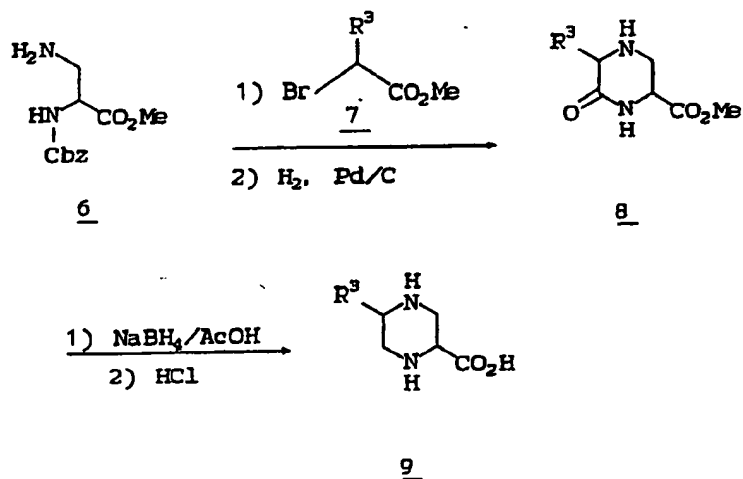
where P is a protecting group

Another route to piperazine-2-carboxylic acids is illustrated in Scheme 3. The α -Cbz-protected α,β -diamino ester 6 is reacted with α -bromo ester 7. Following hydrogenolysis of the Cbz group, the oxopiperazinecarboxylate 8 is obtained. Selective reduction and hydrolysis affords the piperazinecarboxylic acid 9. This route [B. Aebischer, *et al.*, *Helv. Chim. Acta*, 72, 1043

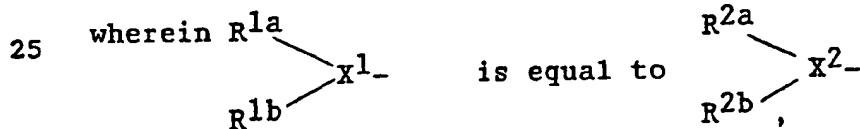
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(1989)] has been used (for $R^3=H$) to prepare chiral piperazine-2-carboxylic acid from a chiral diamino ester 6. Optically active piperazine-2-carboxylic acids have also been obtained from the racemate via a camphorsulfonic acid salt [E. Felder, Helv. Chim. Acta, 43, 888 (1960)] or menthyl ester [B. Aebischer, et al., Helv. Chim. Acta, 72, 1043 (1989)].

SCHEME 3



For the subclass of compounds of formula I



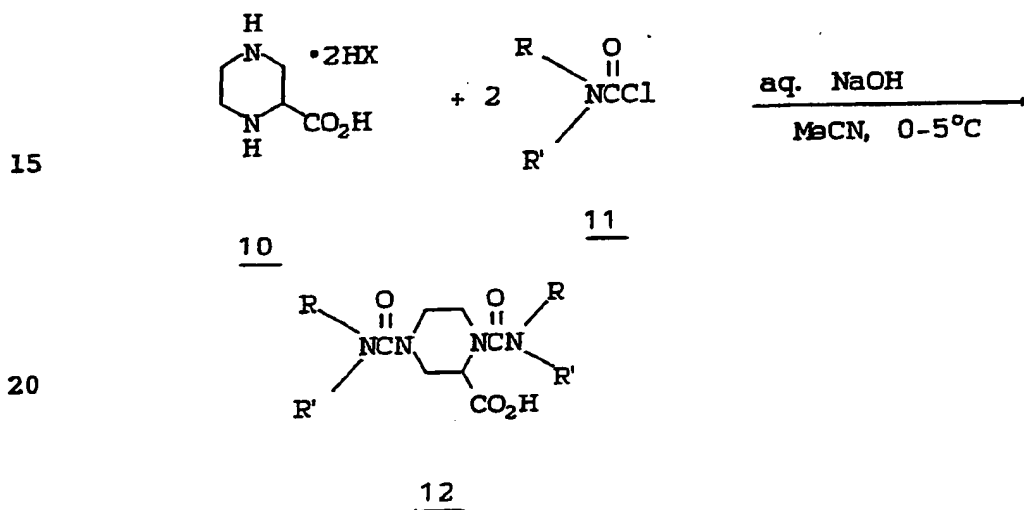
the acylation (or carbamoylation) of the piperazine nucleus may be accomplished straightforwardly in a single step. An example is shown in Scheme 4. Thus piperazine-2-carboxylic acid dihydrohalide (10) [F.L. Bach, Jr., et al., J. Am. Chem. Soc., 77, 6049

- 50 -

(1955); E. Felder, *et al.*, Helv. Chim. Acta, 43, 888 (1960)] in the presence of excess aqueous sodium hydroxide and a cosolvent such as acetonitrile may be treated with two equivalents of a carbamoyl chloride 11, preferably at about 0-5°C to afford the product 12. A similar reaction can be carried out with an acid chloride analogous to 11 in which N is replaced by CH.

SCHEME 4

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25 where R = R^{1a} = R^{2a},
 R' = R^{1b} = R^{2b} and
 X = Cl, Br, etc.

30 If $\begin{matrix} R^{1a} \\ R^{1b} \end{matrix} \begin{matrix} \diagup \\ \diagdown \end{matrix} X^1$ does not equal $\begin{matrix} R^{2a} \\ R^{2b} \end{matrix} \begin{matrix} \diagup \\ \diagdown \end{matrix} X^2$,
 the acylations (or carbamoylations, etc.) are

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performed in stepwise fashion. In the case of piperazine-2-carboxylic acid, a very useful method is to prepare a copper(II) complex, which blocks N¹ and allows the regiospecific synthesis of the N⁴-Cbz derivative. After removal of copper(II), N¹ may then
5 be acylated or carbamoylated. Upon deprotection to remove the Cbz group, N⁴ is then available for introduction of a new acyl or carbamoyl group.

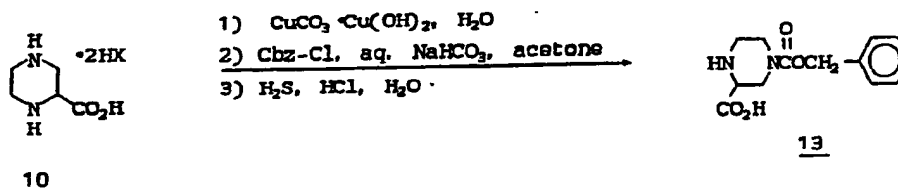
Such a pathway is illustrated in Scheme 5. By the method of M.E. Freed and J.R. Potoski [U.S. Patent 4,032,639 (1977)], 10 is treated with basic cupric carbonate to generate the copper(II) complex, then reacted with Cbz-chloride in the presence of aqueous sodium bicarbonate and acetone, and finally
15 treated with H₂S gas in the presence of aqueous HCl to break down the copper(II) complex, liberating 4-(benzyloxycarbonyl)-2-piperazinecarboxylic acid (13). Variations include the use of cupric chloride at pH 9.5 to form the copper(II) complex and the use
20 of Dowex 50 (H⁺ form) to ultimately remove the copper(II) ion. Treatment of 13 with acylating agent 14 in the presence of base (for example, aqueous sodium hydroxide in acetone or a tertiary amine in DMF or THF) gives 15. The Cbz group of 15 is removed
25 by hydrogenation using palladium on carbon as catalyst in a solvent such as acetic acid, yielding 16. An alternative method of Cbz removal, the use of anhydrous HBr in acetic acid, is preferred when R^{1a} and/or R^{1b} in 15 contain functional groups unstable to hydrogenation. Next, 16 is treated with reagent
30 17 which may be, for example, a carbamoyl chloride, a carboxylic acid N-hydroxysuccinimide ester, an acyl

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imidazolidine, or a carboxylic acid chloride. This reaction is preferably conducted in the presence of a tertiary amine base such as triethylamine or N,N-diisopropylethylamine in a solvent such as THF or DMF. The reaction is typically conducted at about 20-50°C or, in the case of a carboxylic acid chloride, at about 0°C, to give the product 18.

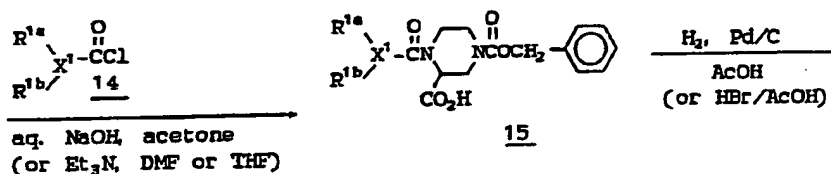
SCHEME 5

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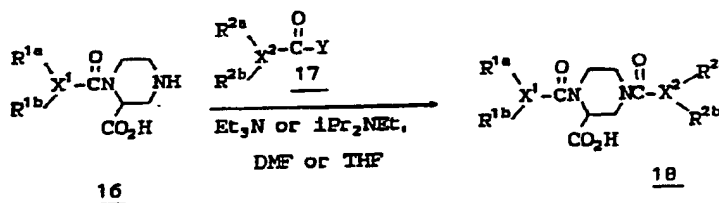


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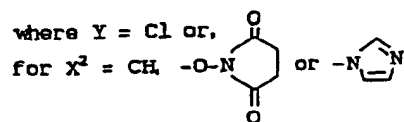
where X=Cl, Br, etc.



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It is sometimes advantageous to avoid the intermediacy of Cbz protection in the synthesis of compounds of structure 18. In Scheme 6, a salt of

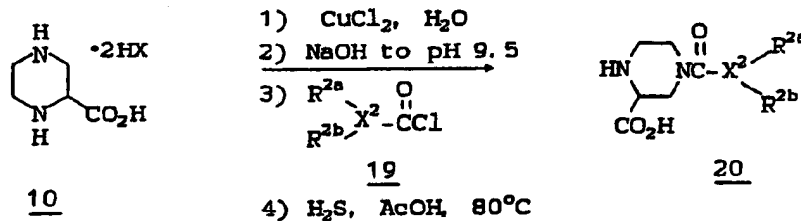
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piperazine-2-carboxylic acid (10) is converted in situ to the copper(II) complex and then treated directly with acylating agent 19 (equivalent to 17 where Y=Cl) in acetone in the presence of aqueous sodium hydroxide. Subsequent treatment with H₂S in acetic acid at about 80°C liberates 20. Reaction of 20 with acylating agent 14 (for example, in DMF in the presence of a base such as N,N-diisopropylethylamine) affords 18.

SCHEME 6

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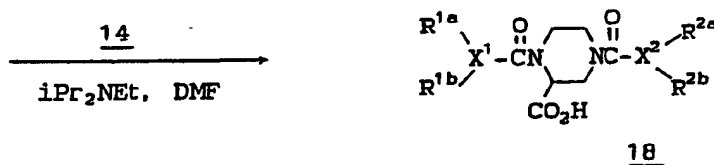
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where X=Cl, Br, etc.

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Mono-N-protected piperazine-2-carboxylate esters are also useful intermediates for the synthesis of compounds of formula I. Thus, intermediates 21 [H. Sugihara and K. Nishikawa, European Patent

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Application EP 368,670 (1990)], 22 (Sugihara and Nishikawa, op. cit.), 23 (Sugihara and Nishikawa, op. cit.), and 24 [C.F. Bigge, et al., Tetrahedron Lett., 30, 5193 (1989)] may all be subjected to an acylation-deprotection-acylation sequence to give 25, as shown in Scheme 7. Acylation (or carbamoylation, etc.) conditions are as described above. The Cbz group is generally removed by catalytic hydrogenation, as discussed above, whereas the Boc group is generally removed either with anhydrous trifluoroacetic acid (neat or in methylene chloride) or with anhydrous HCl in a solvent such as ethyl acetate.

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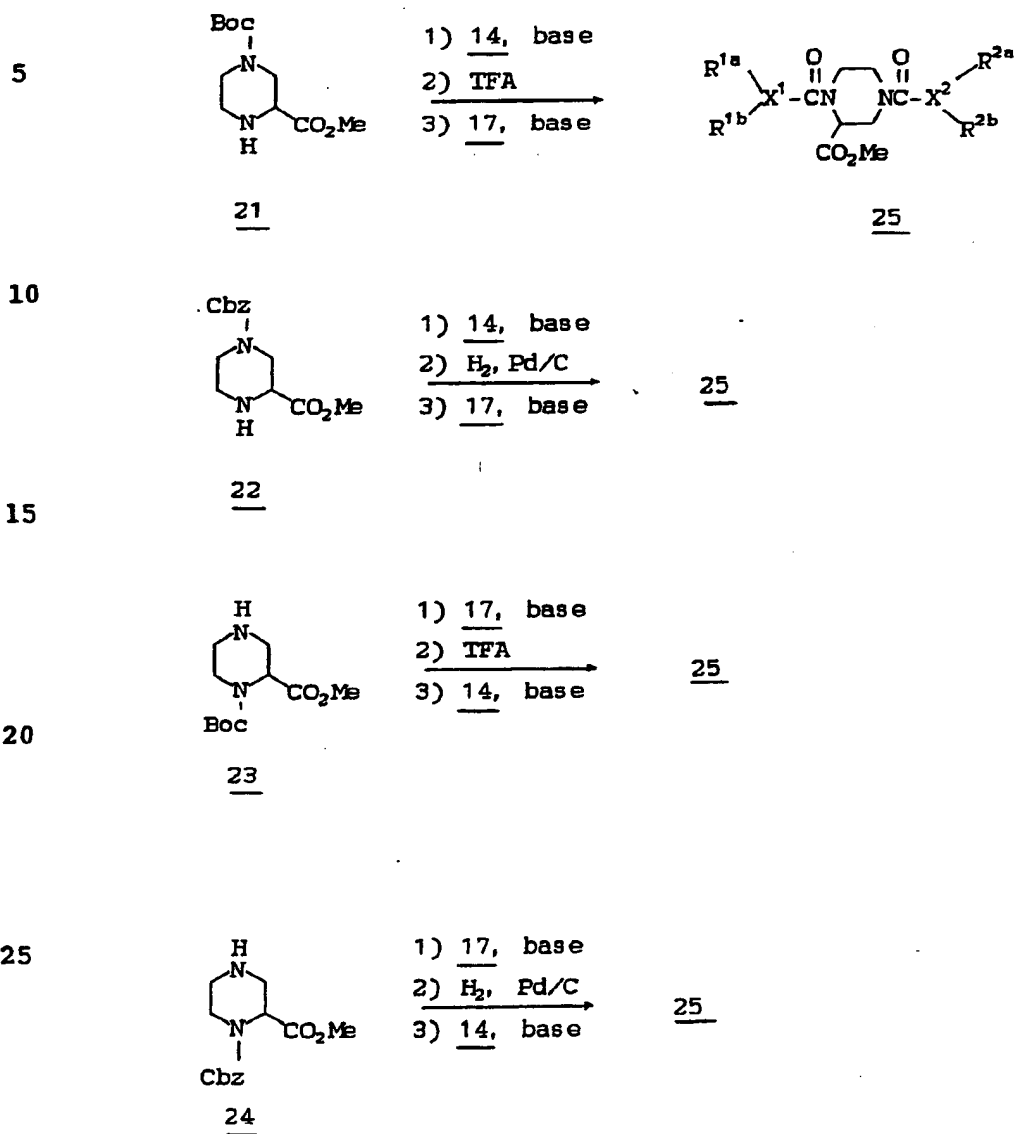
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- 55 -

SCHEME 7



- 56 -

Reagents such as 14, 17, or 19 for acylation (or carbamoylation or oxycarbonylation) of the piperazine are prepared by methods well known in the literature. Several of these standard methods are shown in Scheme 8. For example, a secondary amine 26 is reacted with phosgene to give the carbamoyl chloride 27. The reaction may be carried out either by heating a solution of the amine and phosgene in toluene at about 90°C or by conducting the reaction in a two-phase system of toluene and aqueous sodium hydroxide at about -5°C. In the case of primary amine 28 (equivalent to 26 where $R^b=H$), heating with phosgene in toluene yields the isocyanate 29, which can be reacted with a piperazine derivative in the same fashion as a carbamoyl chloride. One route to an N-aryl-N-alkyl(or aralkyl)carbamoyl chloride 33 is via reductive alkylation. Thus arylamine 30 and aldehyde 31 are reacted in the presence of sodium borohydride in a solvent such as ethanol to give the secondary amine 32, which is converted to 33 with phosgene as described above.

The N,N-diarylcarbamoyl chloride 33e is similarly obtained from the diarylamine 33d, which may be obtained via an Ullmann-type coupling. In one variant [cited in D. Schmidling and F.E. Condon, Baskerville Chem. J. City Coll. N.Y., 12, 22 (1963)], the acetanilide derivative 33a is reacted with aryl bromide 33b in the presence of copper and potassium carbonate neat or in nitrobenzene at reflux to give the N,N-diaryl amide 33c, which is then hydrolyzed to 33d (for example, by heating with 70% sulfuric acid or with ethanolic KOH) [H.S. Freeman, J.R. Butler and

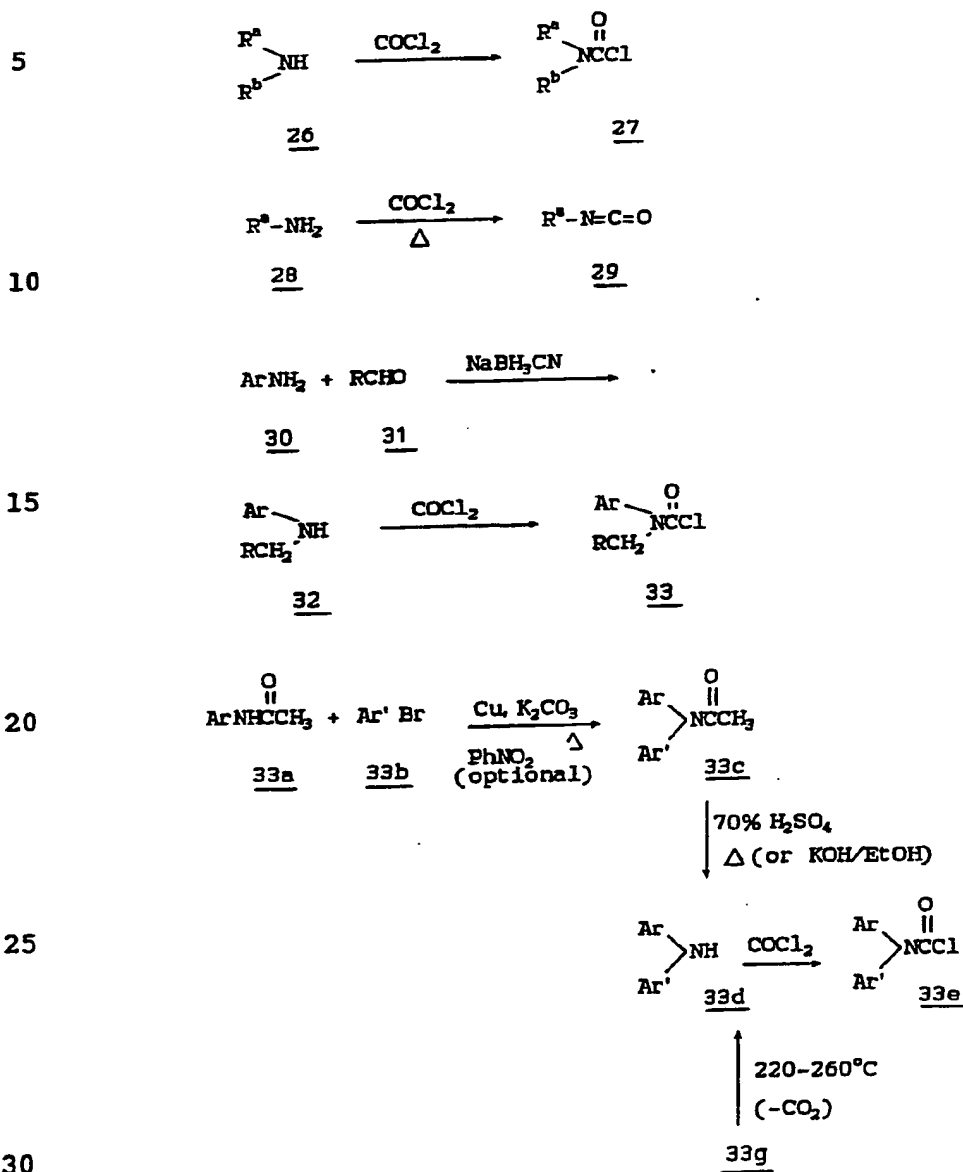
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L.D. Freedman, J. Org. Chem., 43, 4975 (1978)]. In another variant [D. Schmidling and F.E. Condon, op. cit.; S. Kurzepa and J. Cieslak, Roczniki Chem., 34, 111 (1960)], arylamine 30 is coupled with the ortho-bromobenzoic acid derivative 33f by heating at reflux in amyl alcohol in the presence of potassium carbonate and copper. The resulting product 33g, upon heating to about 220-260°C, undergoes decarboxylation to 33d.

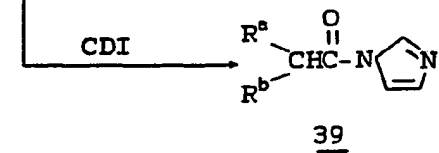
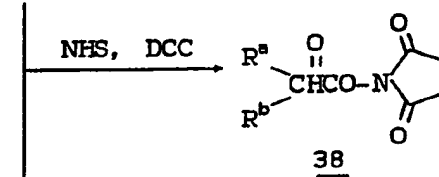
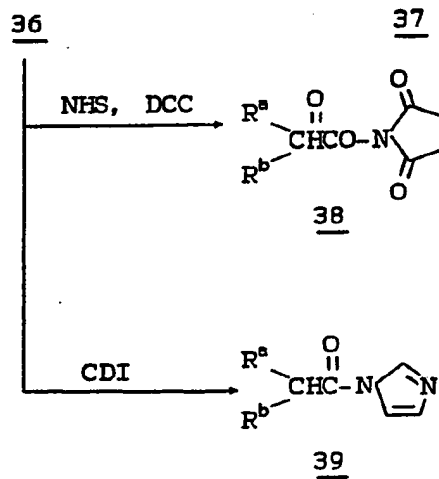
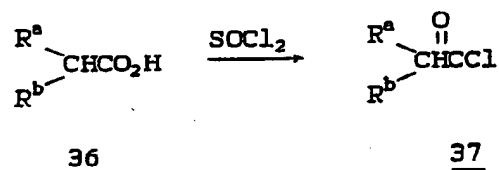
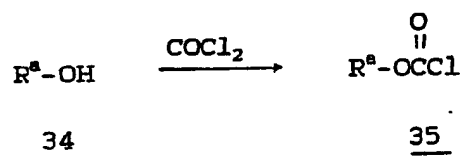
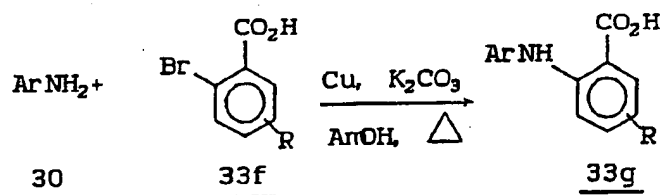
Chloroformate 35 is readily prepared from alcohol 34 with phosgene in toluene, typically at 0-20°C. Carboxylic acid 36 may be converted to the acid chloride 37 by treatment with thionyl chloride (for example in benzene at 80°C). Treatment of 36 with N-hydroxysuccinimide (NHS) in the presence of N,N'-dicyclohexylcarbodiimide (DCC) in a solvent such as acetonitrile provides the reactive N-hydroxysuccinimide ester. The acylimidazolide 39, also a useful acylating agent which may be prepared in situ, is obtained by treatment of 36 with 1,1'-carbonyldiimidazole (CDI) in a solvent such as THF.

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SCHEME 8



SCHEME 8 CONT'D



- 60 -

In compounds of formula 1, the R³ and R⁴ substituents may be present at the time the piperazine ring system is formed, as shown in Schemes 1-3. However, additional transformations may be carried out on the R³ and/or R⁴ functional groups after elaboration of the diacylated (or carbamoylated, etc.) piperazine, as shown in Scheme 9. For example, piperazinecarboxylic acid 40 may be readily converted to its methyl ester 41 by treatment with diazomethane, preferably in ether-methanol or THF at 0-25°C [B. Aebischer, *et al.*, Helv. Chim. Acta, 72, 1043 (1989); C.F. Bigge, *et al.*, Tetrahedron Lett., 30, 5193 (1990)] or by other methods (C.F. Bigge, *et al.*, *op. cit.*). The acid 40 may also be obtained by saponification of 41 under standard conditions. The methyl ester 41 may also be reduced to alcohol 42 by treatment with sodium borohydride/methanol according to the procedures of Sugihara and Nishikawa (EP 0,368,670). Treatment of carboxylic acid 40 with DCC or EDAC/HOBt followed by amine 43 affords the amide 44. Methyl ester 41 may be transformed to aldehyde 45 by use of diisobutylaluminum hydride under controlled conditions at -78°C. Alternatively, alcohol 42 can be oxidized to 45 by various methods, such as the use of catalytic tetrapropylammonium perruthenate (TPAP) and 4-methylmorpholine N-oxide (NMO) in the presence of molecular sieves [W.P. Griffith, *et al.*, J. Chem. Soc. Chem. Commun., 1625 (1987)]. Using standard reductive alkylation conditions, 45 is reacted with amine 43 in the presence of sodium cyanoborohydride to give the aminomethylpiperazine 46. Alcohol 42 may

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be converted to methyl ether 47 by use of dimethyl sulfate, 50% aqueous sodium hydroxide, and a phase transfer catalyst (PTC) such as tetrabutylammonium hydrogen sulfate [A. Merz, Angew. Chem. Int. Ed. Engl., 12, 846 (1973)].

The acylsulfonamide derivative 48 is obtained by treating the carboxylic acid 40 with carbonyldiimidazole and then with the sulfonamide, RSO_2NH_2 , and DBU as base in a solvent such as THF. Treatment of alcohol 42 with the carbamoyl chloride 49 in the presence of a base such as N,N-diisopropylethylamine yields the carbamate 50. Similarly, reaction of 42 with acid chloride 51 in the presence of a base like pyridine gives the acyloxymethylpiperazine 52. The bromomethyl intermediate 53 is available by treatment of alcohol 42 with triphenylphosphine and carbon tetrabromide. Displacement of the bromo group by a thiol 54 occurs in the presence of N,N-diisopropylethylamine as base to give the thioether 55. Oxidation of 55 to the sulfoxide 56 or the sulfone 57 may be carried out with m-chloroperoxybenzoic acid (MCPBA) in a solvent such as methylene chloride or acetic acid. Whether 56 or 57 is the major or exclusive product is dependent on the stoichiometry, reaction time, and temperature.

Besides the methyl ester 41, the carboxylic acid 40 may be converted into other esters 58, for example by treatment with carbonyldiimidazole and an alcohol, ROH, in the presence of catalytic sodium

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ethoxide [H.A. Staab and A. Mannschreck, Chem. Ber.,
95, 1284 (1962)]. An α -(acyloxy)alkyl ester 60 may
be obtained by reaction of 40 with an α -chloralkyl
ester 59 in the presence of triethylamine, sodium
5 iodide, and tetrabutylammonium hydrogen sulfate as
phase transfer catalyst [E.W. Petrillo, et al., U.S.
Patent 4,873,356 (1989)].

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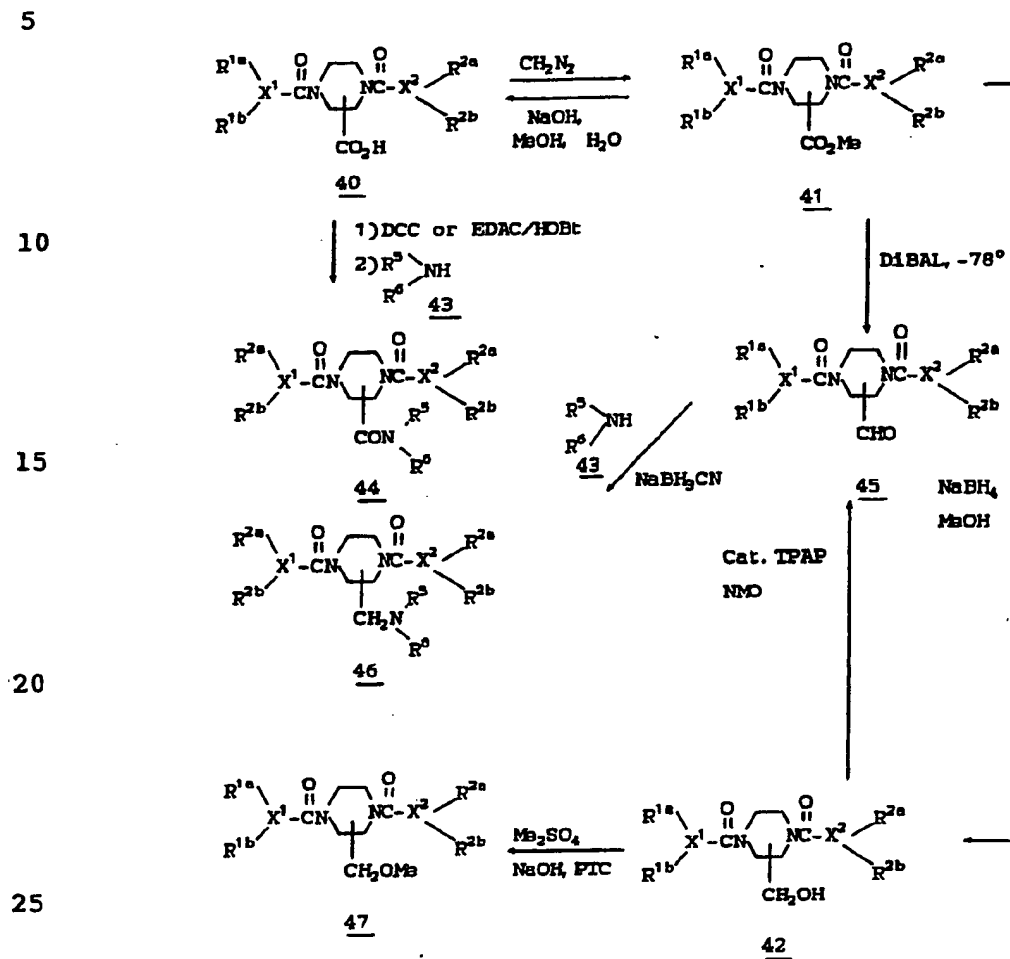
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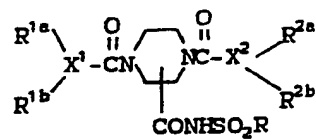
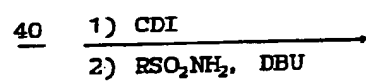
SCHEME 9



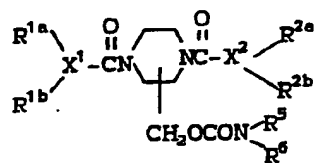
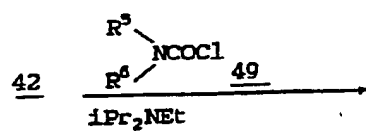
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SCHEME 9 (cont'd.)

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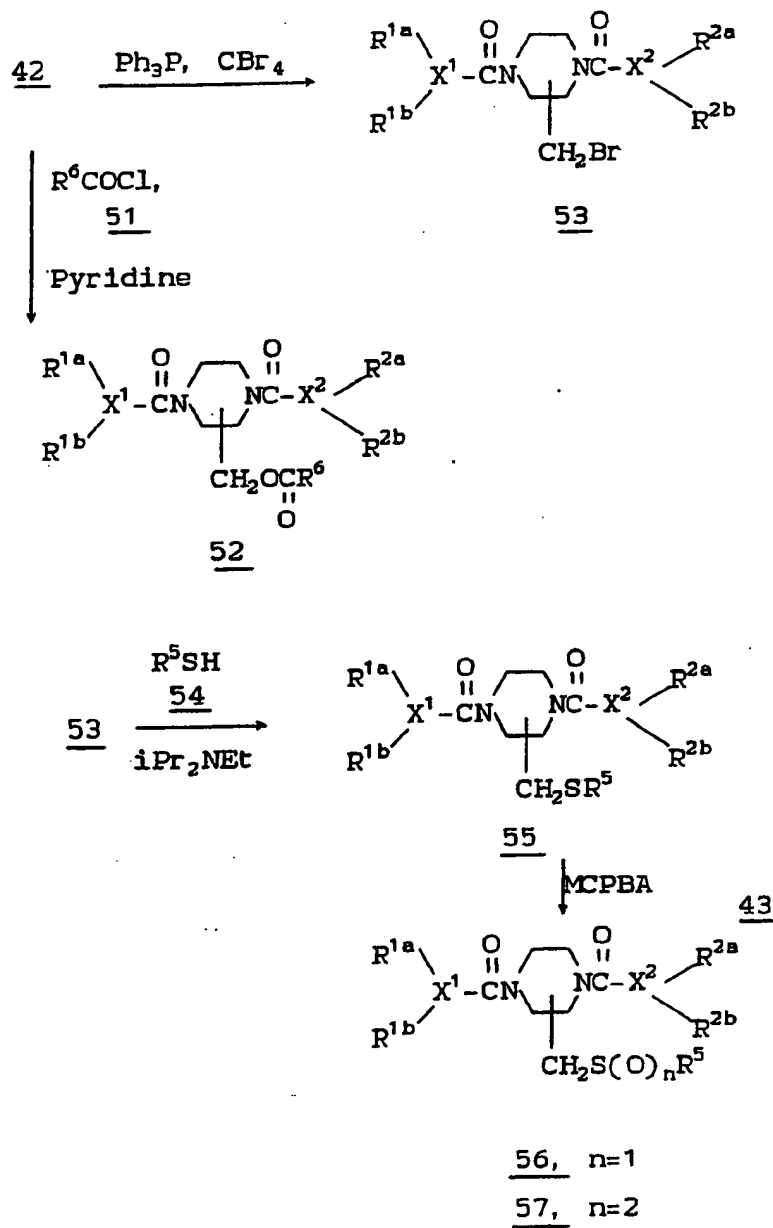
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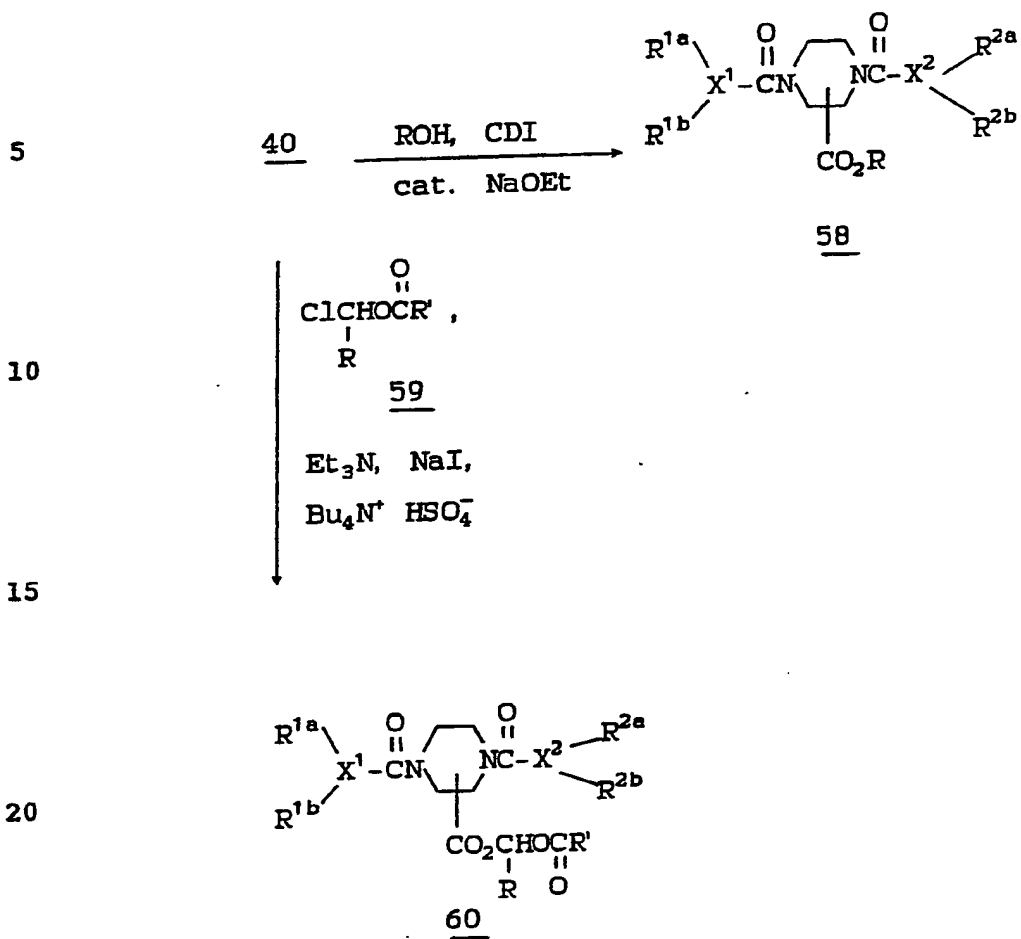
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SCHEME 9 (cont'd.)



- 66 -

SCHEME 9 (cont'd.)

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The object compounds of Formula I obtained according to the reactions as explained above can be isolated and purified in a conventional manner, for example, extraction, precipitation, fractional crystallization, recrystallization, chromatography, and the like.

The compounds of the present invention are capable of forming salts with various inorganic and organic acids and bases and such salts are also within the scope of this invention. Examples of such acid addition salts include acetate, adipate, benzoate, benzenesulfonate, bisulfate, butyrate, citrate, camphorate, camphorsulfonate, ethanesulfonate, fumarate, hemisulfate, heptanoate, hexanoate, hydrochloride, hydrobromide, hydroiodide, methanesulfonate, lactate, maleate, methanesulfonate, 2-naphthalenesulfonate, oxalate, pamoate, persulfate, picrate, pivalate, propionate, succinate, tartrate, tosylate, and undecanoate. Base salts include ammonium salts, alkali metal salts such as sodium, lithium and potassium salts, alkaline earth metal salts such as calcium and magnesium salts, salts with organic bases such as dicyclohexylamine salts, N-methyl-D-glucamine, and salts with amino acids such as arginine, lysine and so forth. Also, the basic nitrogen-containing groups may be quaternized with such agents as: lower alkyl halides, such as methyl, ethyl, propyl, and butyl chloride, bromides and iodides; dialkyl sulfates like dimethyl, diethyl, dibutyl; diamyl sulfates; long chain halides such as decyl, lauryl, myristyl and stearyl chlorides,

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bromides and iodides; aralkyl halides like benzyl bromide and others. The non-toxic physiologically acceptable salts are preferred, although other salts are also useful, such as in isolating or purifying the product.

5 The salts may be formed by conventional means, such as by reacting the free base form of the product with one or more equivalents of the appropriate acid in a solvent or medium in which the salt is insoluble, or in a solvent such as water
10 which is removed in vacuo or by freeze drying or by exchanging the anions of an existing salt for another anion on a suitable ion exchange resin.

 Although the reaction schemes described
15 herein are reasonably general, it will be understood by those skilled in the art of organic synthesis that one or more functional groups present in a given compound of formula I may render the molecule incompatible with a particular synthetic sequence.
20 In such a case an alternative route, an altered order of steps, or a strategy of protection and deprotection may be employed. In all cases the particular reaction conditions, including reagents, solvent, temperature, and time, should be chosen so
25 that they are consistent with the nature of the functionality present in the molecule.

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EXAMPLE 1(±)-4-(Benzyloxycarbonyl)-1-(diphenylacetyl)-2-piperazinecarboxylic acid

5 A solution of 2.64 g (10 mmole) of
 (±)-4-benzyloxycarbonyl)-2-piperazinecarboxylic acid
 [M.E. Freed and J.R. Potoski, U.S. Patent 4,032,639
 (1977)] in 11.2 ml (11.2 mmole) of 1N NaOH was
10 diluted with 11.2 ml of acetone. This solution was
 stirred vigorously at room temperature as a solution
 of 2.31 g (10 mmole) of diphenylacetyl chloride in 10
 ml of acetone was added dropwise in portions,
 alternating with dropwise addition of small portions
15 of 2.5 N NaOH [as necessary to maintain basic pH;
 total addition, 4 ml (10 mmole)]. After the addition
 was complete and the pH was no longer changing, the
 solution was stirred for approximately 1 hour and
 then filtered to remove a small amount of insoluble
20 material. The filtrate was diluted with 30 ml of H₂O
 and shaken with 50 ml of ether. The aqueous layer
 was separated and acidified with 2.5 N HCl just to
 the point of full separation of a second oily phase.
 The oil was extracted with a mixture of 40 ml of
25 ether and 10 ml of CH₂Cl₂. The organic phase was
 dried over MgSO₄, treated with charcoal, and filtered
 through Celite. Concentration of the filtrate in
 vacuo gave a yellow-orange oil, which partially
 crystallized on standing. Trituration with a few ml
30 of ether resulted in gradual crystallization of the
 remainder. Finally, the crystalline mass was

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collected on a filter, ground to a powder, and washed with small volumes of ether to yield, after drying, 3.19 g (70%) of cream-colored powder, mp 183.5-185.5°C; homogeneous by TLC in 90:10:1 CHCl₃-MeOH-H₂O. The ¹H NMR indicated a mixture of rotameric forms.

Mass spectrum (FAB): m/e 459 (M+1).

Analysis (C₂₇H₂₆N₂O₅•0.25 H₂O):

Calculated: C, 70.04; H, 5.77; N, 6.05

Found: C, 70.03; H, 5.63; N, 5.95

¹H NMR (DMSO-d₆, 300 MHz, ppm): δ 2.84 (br m, 2H), 3.21 (br dd, 1H), 3.73 (br d, 1H), 3.90 (br d, 1H) 4.29 and 4.38 (minor and major br d, 1H total), 4.98 (br m, 1H), 5.04 (s, 2H), 5.54, 5.60 (minor and major s, 1H total), 7.15-7.4 (m, 15 H).

EXAMPLE 2

(±)-4-[(3,4-Dimethoxyphenyl)acetyl]-1-(diphenylacetyl)-2-piperazinecarboxylic acid

Step A: (±)-1-(Diphenylacetyl)-2-piperazinecarboxylic acid

A mixture of 1.00 g (2.18 mmole) of (±)-4-(benzyloxycarbonyl)-1-(diphenylacetyl)-2-piperazinecarboxylic acid (from Example 1), 500 mg of 10% palladium on carbon, and 10 ml of glacial acetic acid was shaken with hydrogen (initial pressure 48 psig) on a Parr apparatus for 44 hours, by which time TLC (90:10:1 CHCl₃-MeOH-H₂O) indicated complete reaction. The mixture was filtered through Celite

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(under N₂), and the filter cake was washed with some additional acetic acid. The combined filtrate and washings were evaporated under a stream of N₂. The residual gum was dissolved in 10 ml of methanol, and the hazy solution was filtered through Celite. The filter cake was washed with an additional 10 ml of methanol (added to original filtrate). The product was induced to crystallize from the filtrate. After refrigeration for 2 or 3 hours, the crystallized solid was collected on a filter and washed with small volumes of methanol and then with ether to give, after drying, 632 mg (89%) of white crystals, mp 183.5-185°C dec.; homogeneous by TLC (4:1:1 BuOH-AcOH-H₂O), visualized by UV and by ninhydrin. The ¹H NMR was complex, indicating a mixture of rotamers about the amide bond.

Mass spectrum (FAB): m/e 325 (M+1).

Analysis (C₁₉H₂₀N₂O₃•1.4 H₂O):

Calculated: C, 65.27; H, 6.57; N, 8.02

Found: C, 65.36; H, 6.68; N, 8.03

¹H NMR (DMSO-d₆, 300 MHz, ppm): δ 2.28-2.40 (m, ~1H), 2.60 (br t, <1H), 2.75 (dd, <1H), 2.89 (br d, <1H), 2.95-3.2 (m, ~1H), 3.41 (br t, <1H), 3.55 (br t, ~1H), 3.83 (br d, <1H), 4.30 (br d, <1H), 4.40 (br s, <1H), 4.85 (fine d, <1H), 5.39, 5.54 (minor and major s, 1H total), 7.1-7.4 (m, 10H).

Step B: (3,4-Dimethoxyphenyl)acetic acid N-hydroxy-succinimide ester

A mixture of 1.96 g (10 mmole) of (3,4-dimethoxyphenyl)acetic acid, 1.15 g (10 mmole) of

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N-hydroxysuccinimide, 2.06 g (10 mmole) of N,N'-dicyclohexylcarbodiimide (DCC) and 20 ml of dry acetonitrile was stirred at ambient temperature in a stoppered flask. Even before all of the starting materials had dissolved, precipitation of
5 N,N'-dicyclohexylurea (DCU) began and soon became heavy, accompanied by a mild exotherm. After 2 days, the DCU was removed by filtration, and the filtrate was concentrated in vacuo. The residual oil was
10 dissolved in a mixture of 40 ml of ether and 10 ml of CH₂Cl₂. This solution was shaken with 25 ml of saturated aqueous NaHCO₃. The organic phase was dried over MgSO₄, diluted with some additional CH₂Cl₂ to prevent crystallization, and filtered.
15 Concentration of the filtrate gave a residual semi-solid, which was triturated thoroughly with ether until full crystallization had occurred. The solid was collected on a filter, washed with small volumes of ether, and dried to yield 2.30 g (78%) of
20 light cream-colored crystals, mp 107.5-108.5°C; satisfactory purity by TLC in 1:1 hexane-EtOAc.
¹H NMR (CDCl₃, 300 MHz, ppm): δ 2.81 (s, 4H), 3.85, 3.88 (s, 8H total), 6.8-6.9 (m, 3H).

25 Step C: (±)-4-[(3,4-Dimethoxyphenyl)acetyl]-1-(diphenylacetyl)-2-piperazinecarboxylic acid
A mixture of 162 mg (0.5 mmole) of (±)-1-(diphenylacetyl)-2-piperazinecarboxylic acid (from Step A), 146 mg (0.5 mmole) of (3,4-dimethoxyphenyl)acetic
30 acid N-hydroxysuccinimide ester (from Step B), 69.6 μl (50.5 mg; 0.5 mmole) of triethylamine, and 0.5 ml

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of dry N,N-dimethylformamide (DMF) was stirred at room temperature in a stoppered flask for 88 hours. The solution was then diluted with 10 ml of ethyl acetate and washed with 4x25 ml of dilute HCl. Because some precipitation had occurred during the washings, additional ethyl acetate and a few ml of tetrahydrofuran (THF) were added. However, the precipitate did not redissolve. The organic layer was separated, dried briefly over $MgSO_4$, and filtered. Concentration of the filtrate gave a residue which solidified upon trituration with a small volume of methanol. The solid was collected on a filter and washed with small volumes of methanol, then with ether. After drying, the yield of white powder was 162 mg (64%), mp 191-192°C dec.; homogeneous by TLC in 90:10:1 CH_2Cl_2 -MeOH-AcOH. The 1H NMR spectrum indicated a complex mixture of rotameric forms.

Mass spectrum (FAB): m/e 503 (M+1).

Analysis ($C_{29}H_{30}N_2O_6 \cdot 0.33 H_2O$):

Calculated: C, 68.49; H, 6.08; N, 5.51

Found: C, 68.58; H, 6.26; N, 5.28

1H NMR (DMSO- d_6 , 300 MHz, ppm): δ 2.5-5.1 (complex series of m's, 15H total, including prominent overlapping OCH_3 singlets centered at 3.71), 5.5-5.65 (m, 1H), 6.6-6.9 (m, 3H), 7.15-7.35 (m, 10H).

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EXAMPLE 3(±)-4-(Dipentylcarbamoyl)-1-(diphenylacetyl)piperazine-2-carboxylic acid5 Step A: Dipentylcarbamoyl chloride

A mixture of 7.86 g. (50.0 mmole) of dipentylamine, 18.05 ml (50.0 mmole) of 2.77M NaOH solution and 60 ml of toluene was vigorously stirred at -7 to -5°C, and 60 ml (115.8 mmole) of 1.93 M phosgene in toluene was added dropwise over 1 hour. After stirring an additional 30 min., the cold mixture was separated and the toluene layer was dried over solid NaCl. After filtering, nitrogen was bubbled through the solution for 1 hour and the solution was concentrated in vacuo to 10.5 g. (95%) of light yellow oil.

IR (cm⁻¹): 1740

Mass spectrum (FAB); m/e 220 (M+1)

20 ¹H NMR (CDCl₃, 400 MHz, ppm): δ 0.91 (overlapping t, 6H), 1.25-1.38 (m, 2H), 1.53-1.67 (m, 4H), 3.32 (t, 2H), 3.37 (t, 2H).

Step B: (±)-4-(Dipentylcarbamoyl)-1-(diphenylacetyl)-piperazine-2-carboxylic acid

25 A mixture of 79 mg (0.24 mmole) of (±)-1-(diphenylacetyl)piperazine-2-carboxylic acid (from Example 2, Step A) and 2 ml of THF was treated with 49 mg (0.48 mmole) of triethylamine to give a solution which was cooled to 0°C. With stirring a solution of 61 mg (0.25 mmole) of dipentylcarbamoyl

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chloride (from Step A) in 0.5 ml of THF was added and the solution was briefly warmed to 50°C and then stirred at 25°C for 16 hours. The resulting mixture was filtered and the filtrate was concentrated in vacuo to an oil which was dissolved in 0.5 ml of methanol and was chromatographed over an 85 x 0.9 cm. LH-20 column with 1.7 ml fractions of methanol. Fractions 21-25 were combined and concentrated in vacuo to 70 mg (57%) of oil.

Mass spectrum (FAB): m/e 508 (M+1)

¹H NMR (CDCl₃, 300 MHz, ppm): δ 0.84 (t, 6H), 1.15-1.35 (m, 8H), 1.38-1.55 (m, 4H), 2.6 (m, 1H), 3.1 (m, 6H), 3.35 (m, 1H), 3.42 (m, 1H), 3.7 (m, 1H), 3.92 and 4.05 (minor and major d, 1H total), 5.17 and 5.21 (minor and major s, 1H), 7.2-7.4 (m, 10H).

EXAMPLE 4

Methyl (±)-4-(Dipentylcarbamoyl)-1-(diphenylacetyl)
piperazine-2-carboxylate

A solution of 23.4 mg (0.046 mmole) of (±)-4-(dipentylcarbamoyl)-1-(diphenylacetyl)piperazine-2-carboxylic acid (from Example 3) in a 1:1 mixture of methanol-diethyl ether was cooled to 0°C with stirring and was treated in a slow stream with 10 ml of ethereal diazomethane which was generated by adding 0.5 g (4.85 mmole) of N-nitrosomethylurea to a mixture of 1.15 g (17.4 mmole) of 85% potassium hydroxide in 1.0 ml of water and 12.5 ml of diethyl-ether at 0°C. The diazomethane slurry was stirred

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briskly for 10 minutes and the yellow ether solution was dried over 1 g of potassium hydroxide pellets prior to addition to the carboxylic acid solution. The resulting yellow solution of the carboxylic acid and diazomethane was allowed to warm to 25°C over 16 hours. Evaporation of the solution gave 24 mg (~100%) of pale yellow oil which was homogeneous by TLC (3:1 hexane-ethyl acetate, $R_f = 0.2$).

Mass spectrum (FAB): m/e 522 (M+1)

^1H NMR (CDCl_3 , 300 MHz, ppm): δ 0.85 (t, 6H), 1.20 (m, 4H), 1.26 (m, 4H), 1.43 (m, 4H), 2.58 (t of d, 1H), 2.98 (t of d, 1H), 3.10 (m, 5H), 3.29 (d, 1H), 3.42 (t of d, 1H), 3.68 (s, 3H) overlapping with 3.68 (m, 1H), 3.84 and 3.99 (minor and major d, 1H total), 5.02 and 5.23 (minor s and major s, 1 H total), 7.2-7.3 (m, 10H).

EXAMPLE 5

(±)-4-(Dipentylcarbamoyl)-1-(diphenylcarbamoyl)piperazine-2-carboxylic acid

Step A: (±)-4-(Benzyloxycarbonyl)-1-(diphenylcarbamoyl)piperazine-2-carboxylic acid

A mixture of 264 mg (1.00 mmole) of (±)-4-(benzyloxycarbonyl)piperazine-2-carboxylic acid (see Example 1), 202 mg (2.00 mmole) of triethylamine and 3 ml of THF was cooled to 0°C, and with stirring 231 mg (1.00 mmole) of diphenylcarbamoyl chloride was added. The mixture was stirred at 25°C for 16 hours and was concentrated in vacuo. After partitioning

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between 20 ml of 1N HCl and 30 ml of ethyl acetate the organic phase was dried over sodium sulfate and was concentrated in vacuo to a waxy solid which was chromatographed over an 85 x 2.5 cm LH 20 column with 11 ml fractions of methanol. Fractions 36-39 were combined and concentrated to 109 mg (24%) of oil which was homogeneous by TLC (ethyl acetate, R_f = 0.08).

Mass spectrum (FAB): m/e 460 ($M+1$)

Analysis ($C_{26}H_{25}N_3O_5 \cdot 0.5 H_2O$):

Calculated: C, 66.59; H, 5.55; N, 8.96

Found: C, 66.90; H, 5.63; N, 8.47.

1H NMR ($CDCl_3$, 300 MHz, ppm): δ 2.6-2.8 (m, 1H), 3.04 (d of d, 1H), 3.21 (m, 1H), 3.63 (d, 1H), 3.83 (m, 1H), 4.56 (d, 1H), 4.76 (s, 1H), 5.12 (s, 2H), 7.08-7.22 (m, 5H), 7.24-7.39 (m, 10H).

Step B: (+)-1-(Diphenylcarbamoyl)piperazine-2-carboxylic acid acetate salt

A solution of 109 mg. (0.24 mmole) of (+)-4-(benzyloxycarbonyl)-1-(diphenylcarbamoyl)piperazine-2-carboxylic acid (from Step A) in 3 ml of methanol containing 3 drops of acetic acid and 50 mg of 10% Pd/C was hydrogenated with rocking at 40 psi of hydrogen for 16 hours. The mixture was filtered through Celite and the solution was concentrated in vacuo to 66 mg (71%) of solid which was homogeneous by TLC (1:1:1:1 n-butyl alcohol-acetic acid-water-ethyl acetate, R_f = 0.70).

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¹H NMR (CDCl₃, 300 MHz, ppm): δ 2.05 (s, 3H), 2.72 (m, 1H), 2.96 (m, 1H), 3.12 (m, 1H), 3.26 (m, 1H), 3.67 (m, 1H), 3.79 (m, 1H), 4.78 (br.s, 1H), 7.0-7.3 (m, 10H).

5 Step C: (+)-4-(Dipentylcarbamoyl)-1-(diphenylcarbamoyl)-piperazine-2-carboxylic acid
A solution of 66 mg (0.17 mmole) of (+)-1-(diphenylcarbamoyl)piperazine-2-carboxylic acid acetate salt (from Step B) and 100 mg (0.99 mmole) of
10 triethylamine in 2 ml of THF was treated with 1 ml of water to dissolve the precipitated salts and was treated with 50 mg (0.23 mmole) of dipentylcarbamoyl chloride (from Example 3, Step A) in 0.3 ml. of THF.
15 The solution was warmed at 50°C for 16 hours. After concentrating in vacuo, the residue was partitioned between 20 ml of 0.1N HCl and 30 ml. of ethyl acetate. The organic phase was dried over sodium sulfate and concentrated to 83 mg. (96%) of pale
20 yellow oil.

Mass spectrum (FAB): m/e 509 (M+1)
¹H NMR (CDCl₃, 300 MHz, ppm): δ 0.88 (t, 6H), 1.27 (m, 8H), 1.48 (m, 4H), 2.67 (m, 1H), 2.91 (d of d, 1H), 3.05 (m, 5H), 3.29 (br.d, 1H), 3.68 (br.d, 1H),
25 3.92 (br.d, 1H), 4.74 (br.s, 1H), 7.1-7.4 (m, 10H).

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EXAMPLE 6

Methyl (\pm) -4-(Dipentylcarbamoyl)-1-(diphenylcarbamoyl)piperazine-2-carboxylate

5 A solution of 22.6 mg (0.044 mmole) of (\pm) -4-(dipentylcarbamoyl)-1-(diphenylcarbamoyl)piperazine-2-carboxylic acid (from Example 5) in 2 ml of diethyl ether was treated with diazomethane according to the procedure described in Example 4. A
10 quantitative yield of 23 mg of pale yellow oil was obtained which was homogeneous by TLC (3:1 hexane-ethyl acetate, $R_f = 0.15$).

Mass spectrum (FAB): m/e 523 (M+1)

15 ^1H NMR (CDCl_3 , 300 MHz, ppm): δ 0.85 (t, 6H), 1.2-1.35 (m, 8H), 1.47 (m, 4H), 2.62 (m, 1H), 2.88 (m, 1H), 3.0-3.3 (m, 6H), 3.68 (m, 1H), 3.73 (s, 3H), 3.84 (d, 1H), 4.77 (s, 1H), 7.05-7.35 (m, 10H).

EXAMPLE 7

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(S) -4-(Dipentylcarbamoyl)-1-(diphenylcarbamoyl)piperazine-2-carboxylic acid

25 Step A: (S) -4-(Benzyloxycarbonyl)piperazine-2-carboxylic acid

A solution of 16.4 g (27.6 mmole) of (S) -piperazine-2-carboxylic acid*2 camphorsulfonic acid [E. Felder, S. Maffei, S. Pietra and D. Pitre, Helv. Chim. Acta, 43, 888 (1960)]* in 60 ml of water
30 was treated with 2.0 g (14.9 mmole) of cupric

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chloride to give a light blue solution. 4.16 g (52 mmole) of 50% sodium hydroxide was added to raise the pH to 9.5 giving a deep blue colored solution. A 60 ml portion of acetone was added and the solution was cooled to 0°C with mechanical stirring. While at 0°, a solution of 6.0 g (33.4 mmole) of 95% benzyl chloroformate in 28 ml of acetone and 28 ml (28 mmole) of 1N sodium hydroxide were added at equal rates over 2 hours to give a slurry of light blue solid in a deep blue solution. After centrifuging, the solid was stirred with 200 ml of 1:1 ethanol-water and was acidified to pH 3 with 6N HCl. The light blue solution was applied to 200 cc of Dowex 50 (H⁺) which was washed with 900 ml of 1:1 ethanol-water until no longer acid. The column was washed with 600 ml of 6:97:97 pyridine-ethanol-water, and the product was eluted with 800 ml of the same solvent. The solution was concentrated to 200 ml in vacuo and the slurry was lyophilized to give 5.09 g (70%) of white solid, mp 198-200°C dec., homogeneous by TLC (1:1:1:1 n-butyl alcohol-acetic acid-water-ethyl acetate, R_f = 0.75; 80:20:2 chloroform methanol-ammonia water, R_f = 0.30).

Mass spectrum (FAB): m/e 265 (M+1)
¹H NMR (DMSO-d₆, 400 MHz, ppm): δ 2.82 (t of d, 1H), 3.0-3.1 (m, 3H), 3.26 (d of d, 1H), 3.89 (d, 1H), 4.19 (d, 1H), 5.08 (s, 2H), 7.3-7.4 (m, 5H).

*Note: The "(-)-piperazine-2-carboxylic acid" obtained by this literature procedure was converted to its dihydrochloride salt,

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having $[\alpha]_D = -5.24^\circ$ ($c = 1.25$, H_2O). This is essentially equal and opposite in sign to the rotation reported for (R)-piperazine-2-carboxylic acid dihydrochloride prepared from a chiral starting material of known absolute configuration [B. Aebischer, *et al.*, Helv. Chim. Acta, **72**, 1043 (1989)]. Thus the configuration of the (-)-piperazine-2-carboxylic acid used here is assigned as (S).

Step B: (S)-4-(Benzyloxycarbonyl)-1-(diphenylcarbamoyl)piperazine-2-carboxylic acid

A solution of 1.03 g (3.90 mmole) of (S)-4-(benzyloxycarbonyl)piperazine-2-carboxylic acid (from Step A) in 12 ml. of DMF was treated with 0.788 g (7.79 mmole) of triethylamine at 25°C. With stirring 0.901 g (3.89 mmole) of diphenylcarbamoyl chloride was added in portions over 2 hours. After 16 hours the mixture was concentrated *in vacuo* to an orange oil which was chromatographed over an 88 x 2.5 cm LH 20 column with 11 ml. fractions of methanol.

Fractions 35-43 were combined and concentrated to 1.136 g (64%) of pale yellow oil which contained a major spot by TLC (80:18:2 chloroform-methanol-ammonia water, $R_f = 0.45$).

Mass spectrum (FAB): m/e 460 (M+1)

1H NMR ($CDCl_3$, 300 MHz, ppm): δ 2.65 (br m, 1H), 3.03 (d of d, 1H), 3.15 (m, 1H), 3.58 (d, 1H), 3.80 (d, 1H), 4.52 (d, 1H), 4.73 (s, 1H), 5.12 (s, 2H), 7.03-7.45 (m, 15H).

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Step C: (S)-1-(Diphenylcarbamoyl)piperazine-2-carboxylic acid acetate salt

A solution of 1.136 g (2.47 mmole) of (S)-4-(benzyloxycarbonyl)-1-(diphenylcarbamoyl)piperazine-2-carboxylic acid (from Step B) and 0.5 ml of acetic acid in 10 ml of methanol was treated with 0.50 g of 10% Pd/C, and the mixture was hydrogenated at 40 psi with rocking for 10 hours. The mixture was filtered and the catalyst was washed with 40 ml of acetic acid at 60°C. The organics were combined, concentrated in vacuo and flushed with 3 x 40 ml of ethyl acetate to give 0.73 g (76%) of white solid which was homogeneous by TLC (1:1:1:1 n-butyl alcohol-acetic acid-water-ethyl acetate, R_f = 0.70; 80:18:2 chloroform-methanol-ammonia water, R_f = 0.10).

Mass spectrum (FAB): m/e 326 (M+1)
 1H NMR (DMSO- d_6 , 200 MHz, ppm): δ 1.90 (s, 3H), 2.9-3.7 (m, 6H), 4.19 (br. s, 1H), 7.02-7.17 (m, 6H), 7.27-7.38 (m, 4H).

Step D: (S)-4-(Dipentylcarbamoyl)-1-(diphenylcarbamoyl)piperazine-2-carboxylic acid

A mixture of 0.73 g (2.05 mmole) of (S)-1-(diphenylcarbamoyl)piperazine-2-carboxylic acid acetate salt (from Step C) and 0.59 g (5.83 mmole) of triethylamine in 15 ml of DMF was treated with dipentylcarbamoyl chloride (from Example 3, Step A) under nitrogen at 50°C with stirring for 2 hours to give a clear solution. The DMF was removed in vacuo over a 50°C bath to leave a yellow oil which was partitioned between 100 ml of 0.2N HCl and 125 ml of

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ethyl acetate. After drying over sodium sulfate the ethyl acetate was removed in vacuo to leave a dark yellow, gummy material which was flash chromatographed over 100 cc of silica gel with 16 x 15 ml fractions of 1:1 (hexane:ethyl acetate) and with 15 ml fractions of methanol. Methanol fractions 5-11 were combined and concentrated. The residue was applied to an 85 x 2.5 cm LH-20 column and eluted with 11 ml fractions of methanol. Fractions 33-38 were combined, concentrated and rechromatographed over LH-20 exactly as before. Fractions 33-39 were combined and concentrated to 124 mg (12%) of glassy gum, homogeneous by TLC (80:20:2 chloroform-methanol-ammonia water, $R_f = 0.5$).

Mass spectrum (FAB): m/e 509 (M+1)

Analysis ($C_{29}H_{40}N_4O_4 \cdot 0.4 H_2O$):

Calculated: C, 67.45; H, 7.91; N, 10.85

Found: C, 67.70; H, 8.03; N, 10.65

1H NMR ($CDCl_3$, 400 MHz, ppm): δ 0.85 (t, 6H), 1.19 (m, 4H), 1.27 (m, 4H), 1.46 (m, 4H), 2.63 (t of d, 1H), 2.91 (d of d, 1H), 3.11 (m, 5H), 3.23 (m, 1H), 3.62 (m, 1H), 3.89 (d, 1H), 4.72 (s, 1H), 7.11 (d, 4H), 7.14 (t, 2H), 7.29 (t, 4H).

EXAMPLE 8

Methyl (S)-4-(dipentylcarbamoyl)-1-(diphenylcarbamoyl)piperazine-2-carboxylate

Following the procedure of Examples 4 and 6 above, 238 mg (0.468 mmole) of (S)-4-(dipentylcarba-

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moyl)-1-(diphenylcarbamoyl)piperazine-2-carboxylic acid (from Example 7) and diazomethane in 10 ml of methanol-ether (1:1), gave a quantitative yield of methyl (S)-4-(dipentylcarbamoyl)-1-(diphenylcarbamoyl)piperazine-2-carboxylate. TLC: R_f 0.85 [Analtech SGF plate developed with isoamyl alcohol-acetone-water (5:2:1)].

Mass spectrum (FAB): m/e 523 (M+1)

1H NMR ($CDCl_3$, 400 MHz, ppm): δ 0.86 (t, 6H), 1.19 (m, 4H), 1.26 (m, 4H), 1.43 (m, 4H), 2.61 (br.t, 1H), 2.88 (m, 1H), 2.99-3.18 (2m, 4H), 3.22 (m, 1H), 3.28 (m, 1H), 3.67 (m, 1H), 3.72 (s, 3H), 3.84 (d, 1H), 4.78 (br.s, 1H), 7.08 (d, 4H), 7.13 (t, 2H), 7.29-7.32 (t, 4H).

EXAMPLE 9

(S)-4-(Dipentylcarbamoyl)-1-(diphenylacetyl)piperazine-2-carboxylic acid

Step A: (S)-4-(Benzyloxycarbonyl)-1-(diphenylacetyl)piperazine-2-carboxylic acid

A solution of 1.00 g (3.78 mmole) of (S)-4-(benzyloxycarbonyl)piperazine-2-carboxylic acid (from Example 7, Step A) in 10 ml of DMF at 25°C was treated with 0.755 g. (7.46 mmole) of triethylamine. The solution was cooled to 0°C and 0.95 g (4.12 mmole) of diphenylacetyl chloride was added in portions over 2 hours. The solution was stirred at 25°C for 64 hours, concentrated in vacuo and partitioned between 60 ml. of 1N HCl and 60 ml of

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ethyl acetate. The ethyl acetate was dried over sodium sulfate, concentrated in vacuo and chromatographed in two portions over an 85 x 2.5 cm LH-20 column with 11 ml fractions of methanol. Fractions 38-41 from both columns were combined and concentrated in vacuo to 785 mg (44%) of oil which was homogeneous by TLC (80:20:2 chloroform-methanol-ammonia water, $R_f = 0.40$).

Mass spectrum (FAB): m/e 459 (M+1)

^1H NMR (CDCl_3 , 400 MHz, ppm): δ 2.68 (m, 1H), 3.16 (m, 1H), 3.38 (m, 1H), 3.72 (m, 1H), 3.88 (m, 1H), 4.51 (m, 1H), 4.66 (d, 1H), 5.21 (s, 1H), 7.17-7.35 (m, 15H).

Step B: (S)-1-(Diphenylacetyl)piperazine-2-carboxylic acid acetate salt

A solution of 785 mg (1.71 mmole) of (S)-4-(benzyloxycarbonyl)-1-(diphenylacetyl)piperazine-2-carboxylic acid (from Step A) in 25 ml of methanol was treated with 800 mg of 10% Pd/C and the mixture was hydrogenated at 40 psi at 25°C with rocking for 4 hours. The mixture was filtered and the catalyst was washed with 4 x 30 ml of acetic acid. All organic phases were combined, concentrated in vacuo, redissolved in 100 ml of water and reconcentrated in vacuo to leave 404 mg (73%) of waxy solid which was homogeneous by TLC (4:1:1 n-butyl alcohol-acetic acid-water, $R_f = 0.55$).

Mass spectrum (FAB): m/e 325 (M+1)

^1H NMR (CD_3OD , 400 MHz, ppm): δ 1.98 (s, 3H), 2.39 (m, 1H), 2.91 (t of d, 1H), 3.02 (m, 1H), 3.15 (m, 1H), 3.55 (m, 1H), 3.84 and 4.03 (two d, 1H total), 4.61 (m, 1H), 5.52 (d, 1H), 7.15-7.42 (m, 10H).

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Step C: (S)-4-(Dipentylcarbamoyl)-1-(diphenylacetyl)-
piperazine-2-carboxylic acid

A solution of 404 mg (1.05 mmole) of (S)-1-(diphenylacetyl)piperazine-2-carboxylic acid acetate salt (from Step B) and 483 mg (3.74 mmole) of N,N-diisopropylethylamine in 8 ml of DMF at 0°C was
5 treated with stirring under nitrogen with 273 mg. (1.25 mmole) of dipentylcarbamoyl chloride (from Example 3, Step A). The solution was stirred at 25°C for 16 hours and was concentrated in vacuo. The
10 residue was partitioned between 20 ml of 1N HCl and 50 ml. of chloroform. The chloroform phase was dried over sodium sulfate and concentrated to a yellow oil which was chromatographed in two parts over an 85
15 x 2.5 cm LH-20 column with 10 ml. fractions of methanol. Fractions 31-34 were combined from each and concentrated in vacuo to give 404 mg (76%) of pale colored oil which was homogeneous by TLC
(80:20:2 chloroform-methanol-ammonia water, R_f =
20 0.55).

Mass spectrum (FAB): m/e 508 (M+1)
 ^1H NMR (CDCl_3 , 400 MHz, ppm): δ 0.86 (m, 6H), 1.18
(m, 4H), 1.24 (m, 4H), 1.46 (m, 4H), 2.58 (t of d,
1H), 2.94 (m, 1H), 3.10 (m, 4H), 3.32 (br.d, 1H),
3.38 (m, 1H), 3.71 (m, 1H), 3.94 and 4.04 (minor d
25 and major d, 1H total), 4.43 (d, 1H), 5.22 (s, 1H),
7.17-7.37 (m, 10H).

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EXAMPLE 10

Methyl (S)-4-(Dipentylcarbamoyl)-1-(diphenylacetyl)-
piperazine-2-carboxylate

- 5 A solution of 368 mg (0.725 mmole) of (S)-4-(
dipentylcarbamoyl)-1-(diphenylacetyl)piperazine-2-
carboxylic acid (from Example 9) in 5 ml of methanol
was treated at 0°C with 20 ml of diazomethane
10 solution in diethyl ether (prepared by the procedure
above). The solution was stirred at 0°C for 30
minutes and at 25°C for 30 minutes. The excess
diazomethane was destroyed by the dropwise addition
of acetic acid until the solution became colorless.
15 The resulting solution was concentrated in vacuo and
the residue was chromatographed over an 85 x 2.5 cm
LH-20 column and concentrated in vacuo to 225 mg
(59%) of pale colored oil which was homogeneous by
TLC (1:1 hexane-ethyl acetate, R_f = 0.7).
20 Mass spectrum (FAB): m/e 522 (M+1)
 1H NMR (CDCl₃, 400 MHz, ppm): δ 0.87 (t, 6H), 1.16
(m, 4H), 1.27 (m, 4H), 1.43 (m, 4H), 2.58 (t of d,
1H), 2.97-3.16 (m, 5H), 3.28 (d of d, 1H), 3.42 (t of
d, 1H), 3.47 (d, 1H), 3.70 (s, 3H), 3.73 (d, 1H),
25 3.83 and 3.99 (minor d and major d, 1H total), 5.01
and 5.23 (minor s and major s, 1H total), 7.20-7.35
(m, 10H).
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EXAMPLE 11

(S)-1-(N-Pentyl-N-phenylcarbamoyl)-4-(diphenylcarbamoyl)piperazine-2-carboxylic acid

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Step A: N-Pentylaniline

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A solution of 22.6 g (200 mmole) of aniline and 51.7 g (600 mmole) of valeraldehyde in 200 ml of ethanol was treated with stirring under nitrogen at 25°C with a solution of 12.57 g (200 mmole) of sodium cyanoborohydride in 100 ml of ethanol which was added with a syringe pump over 24 hours. The reaction mixture was added dropwise to 500 ml of 2N HCl. The solution was concentrated to 200 ml and then shaken with 300 ml of ethyl acetate. The organic phase was extracted with 300 ml of 1N HCl, and the combined acidic layers were added dropwise to an excess of 1N NaOH to leave a basic solution and an oil which were extracted with 150 ml of ethyl acetate.

15

Concentration gave 28 g of oil which was vacuum distilled. The fractions distilling at 1.5 mm of pressure from 80-95°C were collected to give 4.05 g (12%) of light yellow oil which was homogeneous by TLC (10:1 hexane-ethyl acetate, $R_f = 0.45$).

20

^1H NMR (CDCl_3 , 400 MHz, ppm): δ 0.89 (t, 3H), 1.33 (m, 4H), 1.60 (m, 2H), 3.08 (t, 2H), 6.59 (d, 2H), 6.67 (t, 1H), 7.16 (t, 2H).

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Step B: N-Pentyl-N-phenylcarbamoyl chloride

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A solution of 4.05 g (24.8 mmole) of N-pentylaniline (from Step A) in 45 ml of toluene and

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8.96 ml (24.8 mmole) of 2.77 N NaOH were mechanically stirred at -5°C, and 25.7 ml (49.6 mmole) of 1.93 M phosgene in toluene was added dropwise over 30 minutes while maintaining -5°. After half the phosgene solution had been added, the rate of addition was increased easily. After stirring at -5° for an additional 30 minutes, the phases were separated and the toluene layer was dried over 10 g of solid sodium chloride. Concentration gave 5.5 g (98%) of dark yellow oil.

¹H NMR (CDCl₃, 400 MHz, ppm): δ 0.87 (t, 3H), 1.27 (m, 4H), 1.58 (m, 2H), 3.69 (t, 2H), 7.20 (d, 2H), 7.38 (m, 3H).

Step C: (S)-4-(Diphenylcarbamoyl)piperazine-2-carboxylic acid acetate Salt

A stirred solution of 6.0 g (10.1 mmole) of (S)-piperazine-2-carboxylic acid*2 camphorsulfonic acid (see Example 7, Step A, for reference) in 20 ml of water was treated with a solution of 3.8 g (28.3 mmol) of cupric chloride in 20 ml of water and the pH of the resulting solution was increased to 9.5 with 50% sodium hydroxide. The deep blue solution was cooled to 0 to -5°C and 40 ml of acetone was added. Over 1 hour a solution of 2.38 g (10.27 mmole) of diphenylcarbamoyl chloride in 10 ml of acetone and 10.1 ml of 1N sodium hydroxide were added dropwise with vigorous stirring, and the mixture was stirred at 0°C for 1 hour and at 25°C for 1 hour. The filtered solid was washed with 20 ml portions of water, ethanol and diethyl ether to leave 5.02 g of a

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pale blue solid. The solid was dissolved in a mixture of 60 ml of acetic acid and 20 ml of water. The mixture was warmed to 80°C and hydrogen sulfide was bubbled through it for 1 hour with vigorous stirring. The mixture was cooled to 25°C and the excess hydrogen sulfide was displaced with a stream of nitrogen for 16 hours. The mixture was filtered and the black sulfide was washed with 20 ml of 3:1 acetic acid-water. The combined filtrate and washings were concentrated in vacuo to 3.04 g (7.9 mmole, 79%) of foam which was homogeneous by TLC (5:1:1:1 ethyl acetate-acetic acid-water-n-butyl alcohol, $R_f = 0.3$).
Mass spectrum (FAB): m/e 326 (M+1)

15 Step D: (S)-1-(N-Pentyl-N-phenylcarbamoyl)-4-(diphenylcarbamoyl)piperazine-2-carboxylic acid
A stirred solution of 0.383 g (1.00 mmole) of (S)-4-(diphenylcarbamoyl)piperazine-2-carboxylic acid acetate salt (from Step C) and 0.400 g (3.09 mmole) of N,N-diisopropylethylamine in 6 ml of DMF at 0°C was treated with 0.253 g (1.12 mmole) of N-pentyl-N-phenylcarbamoyl chloride (from Step B) and then was warmed to 25°C for 16 hours. The DMF was removed in vacuo and the residue was partitioned between 20 ml of 1N HCl and 50 ml of chloroform which was dried over sodium sulfate and concentrated in vacuo to a yellow oil. The oil was flash chromatographed over 100 cc of silica gel with 12 x 25 ml of chloroform, 10 x 25 ml of 80:20:2 chloroform-methanol-ammonia water. Fractions 19-26

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were combined and concentrated to 0.338 g (ammonium salt) of clear glass which was homogeneous by TLC (80:20:2 chloroform-methanol-ammonia water, R_f = 0.4). The product was partitioned between 20 ml. of 1N HCl and 30 ml of chloroform which was dried over sodium sulfate and concentrated in vacuo to 0.337 g (72%) of a clear glass.

Mass spectrum (FAB): m/e 515 (M+1)

^1H NMR (CDCl_3 , 400 MHz, ppm): δ 0.82 (t, 3H), 1.22 (m, 4H), 1.46 (m, 1H), 1.59 (m, 1H), 2.29 (m, 1H), 2.77 (m, 2H), 2.96 (m, 1H), 3.39 (d, 1H), 3.52 (m, 1H), 3.71 (m, 1H), 4.19 (d, 1H), 4.35 (s, 1H), 7.03-7.12 (m, 8H), 7.22-7.27 (m, 5H), 7.37 (t, 2H).

EXAMPLE 12

(±)-1,4-Bis(diphenylcarbamoyl)piperazine-2-carboxylic acid

A solution of 946 mg (4 mmole) of 98% diphenylcarbamoyl chloride in 4 ml of acetonitrile was added dropwise to a stirring solution of 406.2 mg (2 mmole) of piperazine-2-carboxylic acid dihydrochloride [E. Felder, S. Maffei, S. Pietra and D. Pitre, Helv. Chim. Acta, **43**, 888 (1960)] in 4 ml of 2.5N sodium hydroxide at a temperature between 0° and 5°C. After the addition was completed, the stirring was continued for 4 hours and the solution was acidified with 2N hydrochloric acid while cooling in an ice bath. The reaction mixture was concentrated under reduced pressure and the residue was extracted

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with chloroform. After washing with water, the chloroform solution was dried over MgSO_4 and concentrated in vacuo. The only product which solidified on cooling was triturated with isopropyl ether to give 270 mg (26%) of (\pm)-1,4-bis-(diphenylcarbamoyl)piperazine-2-carboxylic acid, m.p. 244-246°C.

Mass spectrum (FAB): m/e 521 (M+1)

Analysis ($\text{C}_{31}\text{H}_{28}\text{N}_4\text{O}_4$):

Calculated: C, 71.02; H, 5.42; N, 10.76

Found: C, 71.08; H, 5.37; N, 10.26.

^1N NMR (CDCl_3 , with 2 drops CD_3OD , 400 MHz, ppm): δ 2.58 (t of d, 1H), 2.69 (br.d, 1H), 2.9-3.0 (under methanol, about 1H), 3.39 (d, 1H), 3.64 (d, 1H), 4.20 (d, 1H), 4.51 (s, 1H), 6.92 (d, 4H), 7.01 (d, 4H), 7.08 (t, 2H), 7.20-7.25 (m, 10H).

EXAMPLE 13

1,4-bis(diphenylcarbamoyl)-trans-2,5-dimethylpiperazine

To a stirred solution of diphenylcarbamoyl chloride (2.32 g, 10 mmole) and 1.30 g (10 mmole) of N,N-diisopropylethylamine in 40 ml of chloroform was added 571 mg (5 mmole) of trans-2,5-dimethylpiperazine in 5 ml of chloroform. After stirring for 16 hours at room temperature, the reaction mixture was evaporated under reduced pressure and water added. The chloroform layer was then extracted with 2N HCl and washed with water. After drying and

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concentrating to dryness, the white solid was triturated with isopropyl ether to yield 835 mg. (33%) of 1,4-bis(diphenylcarbamoyl)-~~trans~~-2,5-dimethylpiperazine, m.p. 255-257°C.

5 Mass spectrum (FAB): m/e 505 (M+1)

Analysis (C₃₂H₃₂N₄O₂):

Calculated: C, 76.16; H, 6.39; N, 11.10

Found: C, 75.85; H, 6.39; N, 10.83.

10 EXAMPLE 14

(+)-2-Methyl-1,4-bis(diphenylcarbamoyl)piperazine

15 This compound was prepared in a manner similar to that of Example 13. From 9.27 g (40 mmole) of diphenylcarbamoyl chloride, 5.17 g (40 mmole) of N,N-diisopropylethylamine and 2 g (20 mmole) of (+)-2-methyl piperazine, 4.16 g (42%) of (+)-2-methyl-1,4-bis(diphenylcarbamoyl)piperazine, 20 m.p. 200-202°C was obtained.

Mass spectrum (FAB): m/e 491 (M+1)

Analysis (C₃₁H₃₀N₄O₂):

Calculated: C, 75.89; H, 6.16; N, 11.42

Found: C, 75.59; H, 6.20; N, 11.12.

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EXAMPLE 15

(S)-1-[N-(3-bromophenyl)-N-phenylcarbamoyl]-4-(dipentylcarbamoyl)piperazine-2-carboxylic acid

5 Step A: N-(3-Bromophenyl)-N-phenylcarbamoyl-chloride

A solution of 15.0 g (60.4 mmole) of 3-bromo-diphenylamine [i.e., N-(3-bromophenyl)aniline] [S. Kurzepa and J. Cieslak, Roczniki Chem., 34, 111 (1960)] in 30 ml of toluene and 50 ml (116 mmole) of 1.93 M phosgene in toluene were combined and heated at 90°C under nitrogen for 2 hours with stirring. The red-orange colored solution was cooled, flushed with nitrogen for 2 hours to remove excess phosgene and concentrated in vacuo to 18.0 g (58.0 mmole, 96%) of red-orange oil which was homogeneous by TLC (4:1 hexane-ethyl acetate, $R_f = 0.80$).

15 Mass spectrum (FAB): m/e 310 (M+1)

20 IR (neat, cm^{-1}): 1740

Step B: (S)-4-(Benzyloxycarbonyl)-1-[N-(3-bromophenyl)-N-phenylcarbamoyl]piperazine-2-carboxylic acid

25 A solution of 2.52 g (9.54 mmole) of (S)-4-(benzyloxycarbonyl)piperazine-2-carboxylic acid (from Example 7, Step A) in 45 ml of DMF was treated dropwise with 4.91 g (38.0 mmole) of N,N-diisopropylethylamine followed by the dropwise addition of 3.03 g (9.76 mmole) of N-(3-bromophenyl)-N-phenylcarbamoyl chloride (from Step A). The resulting solution was stirred under nitrogen at 25°C for 66 hours. The solution was then concentrated in vacuo to remove

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excess DMF and base, and the colored syrup was dissolved in 100 ml of diethyl ether. This was extracted with 100 ml and 30 ml portions of 1N HCl and with 30 ml of water. Addition of 75 ml of 5% sodium bicarbonate to the ether solution precipitated an orange oil. After 30 minutes of settling the ether was extracted with a second 50 ml portion of 5% sodium bicarbonate. The aqueous solution and precipitated oil were combined and acidified to pH 1 with 6N HCl. The resulting mixture was extracted with 2 x 100 ml of methylene chloride. The methylene chloride extracts were combined and concentrated in vacuo without drying to give 4.06 g (7.54 mmole, 79%) of foam, homogeneous by TLC (1:1:1:1 n-butyl alcohol-acetic acid-ethyl acetate-water, R_f = 0.95, and 80:20:2 chloroform-methanol-ammonium hydroxide, R_f = 0.48).

Mass spectrum (FAB): m/e 538 (M+1)

^1H NMR (CDCl_3 , 400 MHz, ppm): δ 2.70 (br.s, 1H), 3.06 (d, 1H), 3.17 (t, 1H), 3.57 (d, 1H), 3.85 (br.m, 1H), 4.56 (d, 1H), 4.77 (s, 1H), 5.10 (d, 2H), 7.00-7.38 (m, 14H).

Step C: (S)-1-[N-(3-Bromophenyl)-N-phenylcarbamoyl]-piperazine-2-carboxylic acid

A 2.13 g (3.96 mmole) portion of (S)-4-(benzyloxycarbonyl)-1-[N-(3-bromophenyl)-N-phenylcarbamoyl]piperazine-2-carboxylic acid (from Step B) was dissolved in 40 ml of 30% HBr in acetic acid. After stirring for 1 hour at 25°C, the solution was flushed with nitrogen to remove the excess of HBr. Concentration in vacuo gave an oily residue which was partitioned between 100 ml of methylene chloride and

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100 ml of water. The stirred slurry was neutralized to pH 7 with 10% NaOH solution. After a brief stirring the entire mixture was filtered to collect 1.50 g (3.71 mmole, 94%) of white solid which was homogeneous by TLC (5:1:1:1 ethyl acetate-n-butyl alcohol-ethyl acetate-water R_f = 0.33).

Mass spectrum (FAB): m/e 404 (M+1)

1H NMR (DMSO- d_6 , 400 MHz, ppm): δ 2.58 (br.t, 1H), 2.95 (d, 1H), 3.15 (t of d, 1H), 3.41 (d, 1H), 3.62 (d, 1H), 4.16 (br.s, 1H), 7.00 (d of t, 1H), 7.11 (d, 2H), 7.17 (t, 1H), 7.20-7.28 (m, 3H), 7.35 (t, 2H).

Step D: (S)-1-[N-(3-Bromophenyl)-N-phenylcarbamoyl]-4-(dipentylcarbamoyl)piperazine-2-carboxylic acid

A solution of 1.84 g (3.96 mmole) of (S)-1-[N-(3-bromophenyl)-N-phenylcarbamoyl]piperazine-2-carboxylic acid (from Step C) in 15 ml of DMF was cooled over ice, and 2.07 g (16.0 mmole) of N,N-diisopropylethylamine was added, followed by the dropwise addition of 1.08 g (4.92 mmole) of dipentylcarbamoyl chloride (from Example 3, Step A) in 5 ml of DMF over 1 hour. The solution was warmed, and after stirring 16 hours at 25°C, the solution was concentrated in vacuo. The residue was stirred with 50 ml of 1N HCl which was extracted with 2 x 50 ml of methylene chloride. After concentration in vacuo the residue was mixed with 100 ml of diethyl ether which was extracted with 4 x 30 ml of 5% sodium bicarbonate. A tan oil which precipitated was combined with the aqueous solution, and the mixture was acidified to pH 1.0 with 1N HCl. Extraction with 100 ml of chloroform gave 1.03 g (1.76 mmole, 44%) of tan foam

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which was homogeneous by TLC (80:80:2 chloroform-methanol-ammonium hydroxide, $R_f = 0.45$).

Mass spectrum (FAB): m/e 587 ($M+1$)

1H NMR ($CDCl_3$, 400 MHz, ppm): δ 0.85 (t, 6H), 1.18 (m, 4H), 1.27 (m, 4H), 1.46 (m, 4H), 2.70 (t of d, 1H), 2.90 (d of d, 1H), 3.10 (m, 5H), 3.26 (d, 1H), 3.61 (d, 1H), 3.94 (d, 1H), 4.71 (s, 1H), 7.05 (d of d, 1H), 7.10-7.26 (m, 6H), 7.33 (t, 2H).

EXAMPLE 16

(S)-1-[N-(3-Chlorophenyl-N-phenylcarbamoyl)-4-(dipentylcarbamoyl)piperazine-2-carboxylic acid]

Step A: N-(3-Chlorophenyl)-N-phenylcarbamoyl chloride

Following the procedure of Example 15, Step A, 20.4 g (100 mmole) of 3-chlorodiphenylamine [i.e., N-(3-chlorophenyl)aniline] and phosgene in toluene gave 15.4 g (58%) of N-(3-chlorophenyl)-N-phenylcarbamoyl chloride.

Mass spectrum (FAB): m/e 266 ($M+1$)

IR (neat, cm^{-1}): 1740, no NH absorption.

Step B: (S)-1-[N-(3-Chlorophenyl-N-phenylcarbamoyl)-4-(benzyloxycarbonyl)piperazine-2-carboxylic acid]

A solution of 2.66 g (10 mmole) of N-(3-chlorophenyl)-N-phenylcarbamoyl chloride (from Step A) in 10 ml of chloroform was added dropwise to a stirring solution of 3.24 g (10 mmole) of (S)-4-(benzyloxycarbonyl)piperazine-2-carboxylic acid (from Example 7, Step A), 2.72 g (25 mmole) of chlorotrimethylsilane and 4.91 g (38 mmole) of N,N-diisopropylethylamine in 60 ml of chloroform at

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10°C. The reaction mixture was allowed to warm to room temperature and stirring was continued for 60 hours. The reaction mixture was concentrated in vacuo and water and ether were added. The ethereal solution was extracted with 2N HCl and washed with water until neutral. The organic layer was then extracted with saturated sodium bicarbonate. A tan oil which separated was combined with the aqueous solution, and the mixture was acidified with 2N HCl. The resulting mixture was extracted with methylene chloride, and the organic extract was concentrated in vacuo to give 2.80 g (57%) of white solid, m.p. 100°C (softened >80°C); TLC: R_f 0.60 [Analtech SGF plate developed with isoamyl alcohol-acetone-water (5:2:1)].

Mass spectrum (FAB): m/e 494 (M+1)

Analysis ($C_{26}H_{24}N_3O_5Cl$):

Calculated:	C, 63.22; H, 4.90; N, 8.51
Found:	C, 62.98; H, 4.98; N, 8.34

Step C: (S)-1-[N-(3-Chlorophenyl)-N-phenylcarbamoyl]-piperazine-2-carboxylic acid hydrobromide

1.60 g (3.24 mmole) of (S)-1-[N-(3-chlorophenyl)-N-phenylcarbamoyl]-4-(benzyloxycarbonyl)-piperazine-2-carboxylic acid (from Step B) was dissolved in 16 ml of 30% HBr in acetic acid. After stirring for 16 hours at 25°C, the solution was flushed with nitrogen to remove the excess of HBr. Next the solution was concentrated in vacuo and the residue was triturated with ether. The white solids which separated were recrystallized from methanol-ester to give 1.17 g (82%) of the product, mp 185°C dec.

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Mass spectrum (FAB): m/e 360 (M+1)

Analysis (C₁₈H₁₈N₃O₃Cl•HBr•1.5 H₂O):

Calculated: C, 46.18; H, 4.70; N, 8.98

Found: C, 46.20; H, 4.35; N, 8.66

5

Step D: (S)-1-[N-(3-Chlorophenyl)-N-phenylcarbamoyl]-
4-(dipentylcarbamoyl)piperazine-2-carboxylic
acid

To a suspension of 1.05 g (2.3 mmole) of (S)-
10 1-[N-(3-chlorophenyl)-N-phenylcarbamoyl]piperazine-2-
carboxylic acid hydrobromide (from Step C) in 20 ml
of methylene chloride was added 1.23 g (9.5 mmole) of
N,N-diisopropylethylamine followed by the dropwise
addition of a solution of 523 mg (2.38 mmole) of
15 dipentylcarbamoyl chloride (from Example 3, Step A)
in 5 ml of methylene chloride. After stirring 24
hours at 25°C, the solution was extracted with 2N
HCl, then H₂O and dried over MgSO₄. The dried
methylene chloride solution was concentrated in vacuo
20 and the residue was dissolved in isopropyl ether and
was diluted with petroleum ether (bp. 30-60°C) until
cloudy. The oil which precipitated was then
decanted, redissolved in isopropanol and concentrated
in vacuo to yield 464 mg (36%) of (S)-1-[N-(3-
25 chlorophenyl)-N-phenylcarbamoyl]-4-(dipentylcarba-
moyl)piperazine-2-carboxylic acid as a glassy solid;
TLC showed a single spot, R_f 0.75 (Anal tech SGF
plates developed with isoamyl alcohol:acetone:water
[5:2:1]).

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Mass spectrum (FAB): m/e 542 (M+1)

Analysis (C₂₉H₃₉N₄O₄Cl)

Calculated: C, 64.13; H, 7.24; N, 10.32

Found: C, 63.70; H, 6.85; N, 10.23.

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¹H NMR (CDCl₃, 400 MHz, ppm): δ 0.85 (t, 6H), 1.19 (m, 4H), 1.27 (m, 4H), 1.45 (m, 4H), 2.68 (t of d, 1H), 2.91 (d of d, 1H), 3.11 (m, 4H), 3.19 (m, 1H), 3.28 (d, 1H), 3.62 (d, 1H), 3.92 (d, 1H), 4.74 (s, 1H), 6.99 (d, 1H), 7.06-7.13 (m, 4H), 7.19 (m, 2H), 7.33 (t, 2H).

EXAMPLE 17

(S)-1-(10,11-Dihydro-5H-dibenz[b,f]azepine-5-carbonyl-4-(dipentylcarbamoyl)piperazine-2-carboxylic acid

Step A: (S)-1-(10,11-Dihydro-5H-dibenz[b,f]azepine-5-carbonyl)-4-(benzyloxycarbonyl)piperazine-2-carboxylic acid

Following the procedure of Example 16, Step B, 811 mg (2.5 mmole) of (S)-4-(benzyloxycarbonyl)-piperazine-2-carboxylic acid (from Example 7, Step A) 680 mg (6.26 mmole) of chlorotrimethylsilane, 1.23 g (9.5 mmole) of N,N-diisopropylethylamine and 665 mg (2.5 mmole) of 97% of 10,11-dihydro-5H-dibenz[b,f]-azepine-5-carbonyl chloride, gave 284 mg (24%) of (S)-1-(10,11-dihydro-5H-dibenz[b,f]azepine-5-carbonyl)-4-(benzyloxycarbonyl)piperazine-2-carboxylic acid, mp 185°C (softened >90°C); TLC R_f 0.68 (Analtech SGF plates developed with isoamyl alcohol:acetone:water [5:2:1]).

Mass spectrum (FAB): m/e 486 (M+1)

Analysis (C₂₈H₂₇N₃O₅)

Calculated: C, 69.26; H, 5.61; N, 8.65
Found: C, 69.03; H, 5.36; N, 8.25.

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Step B: (S)-1-(10,11-Dihydro-5H-dibenz[b,f]azepine-5-carbonyl)piperazine-2-carboxylic acid hydrobromide

This compound was prepared in a manner similar to the preparation of Example 16, Step C. From 246 mg (0.5 mmole) of (S)-1-(10,11-dihydro-5H-dibenz[b,f]azepine-5-carbonyl)-4-(benzyloxycarbonyl)-piperazine-2-carboxylic acid (from Step A) and 5 ml of 30% HBr in acetic acid, 202 mg (94%) of (S)-1-(10,11-dihydro-5H-dibenz[b,f]azepine-5-carbonyl)piperazine-2-carboxylic acid hydrobromide, mp 180°C dec., was obtained.

Mass spectrum (FAB): m/e 352 (M+1)

Analysis (C₂₀H₂₁N₃O₃•HBr•2H₂O)

Calculated: C, 51.25; H, 5.55; N, 8.97
Found: C, 51.07; H, 5.48; N, 8.73.

Step C: (S)-1-(10,11-Dihydro-5H-dibenz[b,f]azepine-5-carbonyl)-4-(dipentylcarbamoyl)piperazine-2-carboxylic acid

Following the procedure for the preparation of Example 17, Step D, from 183 mg (0.423 mmole) of (S)-1-(10,11-dihydro-5H-dibenz[b,f]azepine-5-carbonyl)piperazine-2-carboxylic acid hydrobromide (from Step B), 219 mg (0.169 mmole) of N,N-diisopropylethylamine and 112 mg (0.51 mmole) of dipentylcarbamoyl chloride (from Example 3, Step A) gave 107 mg (47%) of (S)-1-(10,11-dihydro-5H-dibenz[b,f]azepine-5-carbonyl)-4-(dipentylcarbamoyl)-piperazine-2-carboxylic acid, mp 121-124°C, TLC R_f 0.75 (Analtech SGF plates developed with isoamyl alcohol:acetone:water[5:2:1]).

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Mass spectrum (FAB): m/e 535 (M+1)

Analysis (C₃₁H₄₂N₄O₄•1/2 H₂O)

Calculated: C, 68.42; H, 7.91; N, 10.30

Found: C, 68.68; H, 7.98; N, 10.14.

5 ¹H NMR (CDCl₃, 400 MHz, ppm): δ 0.84 (t, 6H), 1.18 (m, 4H), 1.28 (m, 6H), 1.44 (m, 4H), 1.82 (m, 1H), 2.52 (br. t, 1H), 2.81 (br, 1H), 2.95 (d of d, 1H), 3.07-3.16 (m, 7H), 3.49 (m, 1H), 3.87 (d, 1H), 4.59 (s, 1H), 7.12-7.23 (m, 6H), 7.42 (d, 2H).

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EXAMPLE 18

(S)-2-[(3-(N,N-Diethylamino)propyl)aminocarbonyl]-4-(N,N-di-n-pentylcarbamoyl)-1-(N,N-diphenylcarbamoyl)-
15 piperazine

A mixture of 204 mg (0.4 mmole) of (S)-1-(N,N-diphenylcarbamoyl)-4-(N,N-di-n-pentylcarbamoyl)-piperazine-2-carboxylic acid and 65 mg (0.42 mmole) of HOBT in 5 mL of THF was treated with 93 mg (0.45 mmole) of DCC at 25°C. After being stirred for
20 30 min, 63 mg (0.48 mmole) of 3-diethylaminopropylamine was added and the mixture was stirred at 25°C for 16 hours. The white precipitate was filtered off and the filtrate was concentrated in vacuo. The
25 residue was extracted with 20 mL of CH₂Cl₂, and the extract washed with 10 mL each of water, saturated aqueous sodium bicarbonate, 1N aqueous hydrochloric acid, and saturated aqueous sodium chloride. The
30 organic phase was dried over magnesium sulfate and concentrated in vacuo to give 241 mg (97%) of an oil which was homogeneous by TLC (R_F 0.75; 5:2:1 isoamyl alcohol:acetone:water).

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Mass Spectrum (FAB): m/Z 621 (M+H, 100%).

¹H NMR (CDCl₃, 400 MHz, ppm): δ 0.85 (t, 6H), 1.02 (t, 6H), 1.1-1.3 (m, 8H), 1.43 (pentet, 4H), 1.68 (m, 2H), 2.5-2.6 (m, 6H), 2.70 (td, 1H), 2.85 (dd, 1H), 3.0-3.4 (8H), 3.66 (br d, 1H), 3.87 (d, 1H), 4.47 (br s, 1H), 7.05-7.15 (m, 6H), 7.25-7.33 (m, 4H), 7.59 (br s, 1H).

EXAMPLE 19

(S)-2-[(4-(N,N-Diethylamino)butyl)aminocarbonyl]-4-(N,N-di-n-pentylcarbamoyl)-1-(N,N-diphenylcarbamoyl)-piperazine

A mixture of 42 mg (0.083 mmole) of (S)-1-(N,N-diphenylcarbamoyl)-4-(N,N-di-n-pentylcarbamoyl)piperazine-2-carboxylic acid and 12 mg (0.091 mmole) of HOBt in 1 mL CH₂Cl₂ was cooled to 0°C under a nitrogen atmosphere and was treated with 22 mg (0.091 mmole) of EDAC. After 5 min the ice bath was removed, and after an additional 30 min stirring at 22°C 24 mg (0.17 mmole) of 4-diethylamino-butylamine was added and the mixture was stirred at 22°C for 24 hours. The mixture was purified by flash chromatography on 16g of silica with 250 mL of 100:8:0.3 CH₂Cl₂:MeOH: ammonia water to give 42 mg (81%) of an oil.

Mass Spectrum (FAB): m/Z 642 (M+H, 100%), 230 (ClPhN(Ph)CO, 15%), 184 (25%), 167 (10%).

¹H NMR (CDCl₃, 400 MHz, ppm): δ 0.85 (t, 6H), 0.99 (t, 6H), 1.15-1.3 (m 8H), 1.45 (pentet, 4H), 2.45-2.6 (m, 6H), 2.66 (t, 1H), 2.79 (dd, 1H), 3.0-3.4 (m, 8H), 3.72 (br d, 1H), 3.91 (d, 1H), 4.48 (br s, 1H), 7.0-7.4 (m, 10H).

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EXAMPLE 20

(S)-2-[(2-Aminoethyl)aminocarbonyl]-4-(N,N-di-n-pentylcarbamoyl)-1-(N,N-diphenylcarbamoyl)piperazine

5 A mixture of 202 mg (0.4 mmole) of
(S)-1-(N,N-diphenylcarbamoyl)-4-(N,N-di-n-pentylcarbamoyl)piperazine-2-carboxylic acid and 59 mg
(0.44 mmole) of HOBt in 4 mL of CH₂Cl₂ was cooled to
0°C and was treated with 107 mg (0.56 mmole) of
10 EDAC. After 5 min, the cooling bath was removed and
after an additional 30 min, the mixture was cooled to
-33°C and was treated with 398 microliters (5.96
mmole) of ethylenediamine. After 10 min the cooling
bath was removed and the mixture stirred at 22°C for
15 24 hours. Most of the volatiles were removed by a
gentle stream of nitrogen and the residue was
purified by flash chromatography on 23 g of silica
gel eluting with 1 liter of 100:9:0.4 CH₂Cl₂:MeOH:
ammonia water to give 125 mg (57%) of an oil.
20 Mass Spectrum (FAB): m/Z 706 (M+matrix, 40%, 551
(M+H, 100%), 196 (60%).
¹H NMR (CDCl₃, 400 MHz, ppm): δ 0.85 (t, 6H), 1.05
(br s, 2H), 1.1-1.3 (m, 8H), 1.45 (pentet, 4H),
2.7-2.85 (m, 4H), 2.9-3.1 (3H), 3.15-3.3 (5H), 3.73
(br d, 1H), 3.97 (d, 1H), 4.50 (s, 1H), 7.1-7.15 (m,
25 6H), 7.25-7.33 (m, 4H), 7.46 (br t, 1H).

EXAMPLE 21

30 (S)-1-[N-(3-Chlorophenyl)-N-phenylcarbamoyl]-2-[(3-(N,N-diethylamino)propyl)aminocarbonyl]-4-(N,N-di-n-pentylcarbamoyl)piperazine

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According to the procedure of Example 19 above, 20 mg (0.037 mmole) of (S)-1-[N-(3-chlorophenyl)-N-phenylcarbamoyl]-4-(N,N-di-n-pentylcarbamoyl)piperazine-2-carboxylic acid, 6 mg (0.041 mmole) of HOBt, 10 mg (0.052 mmole) of EDAC, and 10 mg (0.074 mmole) of 3-diethylaminopropylamine after purification by flash chromatography on 16 g of silica gel with 100:7:0.2 CH₂Cl₂:MeOH: ammonia water provided 17 mg (71%) of an oil.

Mass Spectrum (FAB): m/z 657 (M+H, 40%), 656 (M+H, 60%), 655 (M+H, 100%), 621 (20%), 452 (15%), 230 (10%).

¹H NMR (CDCl₃, 400 MHz, ppm): δ 0.85 (t, 6H), 1.02 (t, 6H), 1.1-1.3 (m, 8H), 1.44 (pentet, 4H), 1.68 (br pentet, 2H), 2.55 (br s, 6H), 2.76 (t, 1H), 2.86 (dd, 1H), 3.0-3.15 (m, 5H), 3.2-3.4 (m, 3H), 3.66 (br d, 1H), 3.87 (d, 1H), 4.44 (br s, 1H), 7.06 (m, 3H), 7.1-7.25 (m, 4H), 7.34 (t, 2H), 7.78 (br s, 1H).

EXAMPLE 22

(S)-1,4-Bis[N-(3-chlorophenyl)-N-phenylcarbamoyl]-2-
[(3-(N,N-diethylamino)propyl)aminocarbonyl]piperazine

Step A: (S)-1,4-Bis[N-(3-chlorophenyl)-N-phenylcarbamoyl]-2-piperazinecarboxylic acid

A suspension of 3.0 g (5 mmole) of (S)-1-(N,N-diphenylcarbamoyl)-4-(N,N-di-n-pentylcarbamoyl)piperazine-2-carboxylic acid in 50 mL of CH₂Cl₂ was treated successively with 1.36 g (12.5 mmole) of chlorotrimethylsilane, 2.67 g (30 mmole) of

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DIEA and 2.67 g (10 mmole) of 3-chlorodiphenylcarbamoyl chloride in 10 mL of CH_2Cl_2 , and the mixture was stirred at room temperature for 92 hours. The solution was washed with 20 mL of 2N HCl, 15 mL of water (twice) and was concentrated in vacuo. The residue was taken up in ether and insoluble material removed by filtration. The filtrate was washed with water and the light orange solid was filtered and dried to give 987 mg (34%); mp 200-203°C; TLC: 5:2:1 Isoamyl alcohol:acetone:water R_f 0.80.
Mass Spectrum (FAB): m/Z 612 (M+Na), 589 (M+H).
Analysis ($\text{C}_{31}\text{H}_{26}\text{N}_4\text{O}_4\text{Cl}_2$):
Calculated: C, 63.16; H, 4.45; N, 9.50.
Found: C, 63.20; H, 4.48; N, 9.41.

Step B: (S)-1,4-Bis[N-(3-chlorophenyl)-N-phenylcarbamoyl]-2-[(3-(N,N-diethylamino)propyl)amino-carbonyl]piperazine

According to the procedure of Example 19 above, 20 mg (0.034 mmole) of (S)-1,4-bis[N-(3-chlorophenyl)-N-phenylcarbamoyl]piperazine-2-carboxylic acid, 5 mg (0.037 mmole) of HOBt, 9 mg (0.047 mmole) of EDAC, and 9 mg (0.068 mmole) of 3-diethylamino-propylamine after purification by flash chromatography on 16 g of silica gel with 100:7:0.2 CH_2Cl_2 : MeOH: ammonia water provided 18 mg (75%) of an oil.
Mass Spectrum (FAB): m/Z 703 (M+H, 5%), 702 (M+H, 15%), 701 (M+H, 45%), 700 (M+H, 100%), 230 (35%).
 ^1H NMR (CDCl_3 , 400 MHz, ppm): δ 1.00 (br s, 6H), 1.70 (br s, 2H), 2.4-2.7 (m, 7H), 2.84 (dd, 1H), 3.04 (br s, 1H), 3.35 (m, 2H), 3.46 (d, 1H), 3.55 (d, 1H), 4.21 (d, 1H), 4.43 (s, 1H), 6.9-7.4 (m, 18H), 7.43 (br s, 1H).

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EXAMPLE 23

5 (S)-1-[N-(3-Chlorophenyl)-N-phenylcarbamoyl]-2-[(4-(N,N-diethylamino)butyl)aminocarbonyl]-4-(N,N-di-n-pentylcarbamoyl)piperazine

According to the procedure of Example 19 above, 40 mg (0.074 mmole) of (S)-1-[N-(3-chlorophenyl)-N-phenylcarbamoyl]-4-(N,N-di-n-pentylcarbamoyl)piperazine-2-carboxylic acid, 11 mg
10 (0.081 mmole) of HOBt, 20 mg (0.103 mmole) of EDAC, and 21 mg (0.147 mmole) of 4-diethylaminobutylamine after purification by flash chromatography on 16 g of silica gel with 100:5:0.2 CH₂Cl₂:MeOH: ammonia water
15 provided 38 mg (81%) of an oil.

Mass Spectrum (FAB): m/Z 669 (M+H, 100%), 230 (ClPhN(Ph)CO, 20%).

¹H NMR (CDCl₃, 400 MHz, ppm): δ 0.85 (t, 6H), 1.00 (br s, 6H), 1.1-1.35 (m, 8H), 1.4-1.55 (m, 8H),
20 2.3-2.7 (m, 6H), 2.7-3.05 (m, 5H), 3.1-3.33 (m, 5H), 3.70 (d, 1H), 3.95 (d, 1H), 4.42 (br s, 1H), 7.08 (m, 3H), 7.1-7.3 (m, 4H), 7.34 (t, 2H), 7.52 (br s, 1H).

EXAMPLE 24

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(S)-2-[(3-(N,N-Diethylamino)propyl)aminocarbonyl]-4-(N,N-di-n-pentylcarbamoyl)-1-[N-(3-methylphenyl)-N-phenylcarbamoyl]piperazine

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Step A: N-(3-Methylphenyl)-N-phenylcarbamoyl
chloride

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According to the procedure of Example 15, Step A, 3.66 g (20 mmole) of 3-methyldiphenylamine, 20 mL (38.6 mmole) of 1.93M phosgene in toluene solution, and 20 mL of toluene gave 4.9 g (100%) of a dark solid.

5 Mass Spectrum (FAB): m/Z 245 (M, 67%), 210 (M-Cl, 100%), 182 (M-COCl, 62%), 167 (M-COCl-CH₃, 65%).

10 Step B: (S)-4-(benzyloxycarbonyl)-1-[N-(3-methylphenyl)-N-phenylcarbamoyl]-piperazine-2-carboxylic acid

A mixture of 264 mg (1 mmole) of (S)-4-(benzyloxycarbonyl)piperazine-2-carboxylic acid, 265 mg (1.1 mmole) of N-(3-methylphenyl)-N-phenylcarbamoyl chloride, 390 mg (3 mmole) of DIEA in 15 5 mL of DMF was stirred for 16 hr at room temperature. The solution was concentrated in vacuo and the residue was taken up in 50 mL of CH₂Cl₂ and washed with 2x25 mL of 1N HCl. Concentration in vacuo gave 20 0.55 g of an oil, which was carried on in Step C.

Mass Spectrum (FAB): m/Z 496 (M+Na), 474 (M+1), 210 (MePhN(Ph)CO), 184 (MePhNPh).

25 NMR (CDCl₃, 400 MHz, ppm): δ 2.28 (s, 3H), 2.5-2.7 (m, 1H), 3.0-3.2 (m, 2H), 3.55 (m 1H), 3.79 (br s, 1H), 4.53 (br d, 1H), 4.70 (br s, 1H), 5.0-5.15 (m, 2H), 6.8-7.4 (M, 14H).

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Step C: (S)-1-[N-(3-methylphenyl)-N-phenylcarbamoyl]-
piperazine-2-(S)-carboxylic acid acetate salt

A mixture of 0.55 g (ca. 1.17 mmole; crude from Step B above) of (S)-4-(benzyloxycarbonyl)-1-[N-(3-methylphenyl)-N-phenylcarbamoyl]-piperazine-2-carboxylic acid and 10 mL of 30% HBr in acetic acid was stirred overnight at room temperature. The mixture was flushed with nitrogen to remove excess HBr and was then concentrated in vacuo. The product, which partially crystallized over several days, was carried on in Step D.

Step D: (S)-1-[N-(3-methylphenyl)-N-phenylcarbamoyl]-4-(N,N-di-n-pentylcarbamoyl)piperazine-2-carboxylic acid

According to the procedure of Example 7, Step D, ca. 1 mmole of (S)-1-[N-(3-methylphenyl)-N-phenylcarbamoyl]-piperazine-2-(S)-carboxylic acid acetate salt (crude from Step C above), 388 mg (3 mmole) of DIEA, 329 mg (1.5 mmole) of N,N-di-n-pentylcarbamoyl chloride in 8 mL of DMF to give 83 mg of an oil.

Mass Spectrum (FAB): m/z 680 (10%), 567 (M+2Na - H, 30%), 545 (M+Na, 100%), 523 (M+H, 70%), 517 (45%), 362 (M-[CH₃(CH₂)₄]₂NCO+Na+H, 45%), 294 (M-[CH₃(CH₂)₄]₂NCO-CO₂, 40%), 210 (MePhN(Ph)CO, 83%).

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NMR (CDCl₃, 400 MHz, ppm): δ 0.80 (m, 6H), 1.1-1.35 (m, 8H), 1.45 (pentet, 4H), 2.29 (s, 3H), 2.66 (t, 1H), 2.8-3.0 (m, 2H), 3.05-3.25 (m, 6H), 3.61 (d, 1H), 3.90 (d, 1H), 4.70 (s, 1H), 6.88-7.00 (m, 3H), 7.05-7.35 (m, 6H).

Step E: (S)-2[(3-(N,N-diethylamino)propyl)aminocarbonyl]-4-(N,N-di-n-pentylcarbamoyl)-1-[N-(3-methylphenyl)-N-phenylcarbamoyl]piperazine

According to the procedure of Example 19 above, 26 mg (0.050 mmole) of (S)-1-[N-(3-methylphenyl)-N-phenylcarbamoyl]-4-(N,N-di-n-pentylcarbamoyl)piperazine-2-carboxylic acid, 8 mg (0.055 mmole) of HOBT, 13 mg (0.070 mmole) of EDAC, and 14 mg (0.100 mmole) of 3-diethylaminopropylamine after purification by flash chromatography on 16 g of silica gel with 100:7:0.2 CH₂Cl₂:MeOH: ammonia water provided 20 mg (62%) of an oil.

Mass Spectrum (FAB): m/Z 636 (~M+H, 100%), 210 (MePhN(CO)Ph, 30%).

¹H NMR (CDCl₃, 400 MHz, ppm): δ 0.85 (t, 6H), 1.04 (t, 6H), 1.15-1.35 (t, 8H), 1.44 (pentet, 4H), 1.72 (br s, 2H), 2.28 (s, 3H), 3.5-3.75 (m, 7H), 3.89 (dd, 1H), 3.0-3.30 (m, 7H), 3.34 (m, 1H), 3.66 (d, 1H), 3.89 (d, 1H), 4.48 (br s, 1H), 6.9-7.0 (m, 3H), 7.1-7.35 (m, 6H), 7.55 (br s, 1H).

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EXAMPLE 25

5 (S)-1-[N-(3-Chlorophenyl)-N-phenylcarbamoyl]-2-[(2-(N,N-diethylamino)ethyl)aminocarbonyl]-4-(N,N-di-n-pentylcarbamoyl)piperazine

According to the procedure of Example 19 above, 40 mg (0.074 mmole) of (S)-1-[N-(3-chlorophenyl)-N-phenylcarbamoyl]-4-(N,N-di-n-pentylcarbamoyl)piperazine-2-carboxylic acid, 11 mg
10 (0.081 mmole) of HOBt, 20 mg (0.103 mmole) of EDAC, and 21 mg (0.147 mmole) of 2-diethylaminoethylamine after purification by flash chromatography on 16 g of silica gel with 100:5:0.2 CH₂Cl₂:MeOH: ammonia water provided 38 mg (81%) of an oil.

15 Mass Spectrum (FAB): m/Z 642 (M+H, 100%), 230 (C1PhN(Ph)CO, 15%), 184 (25%), 167 (10%).

¹H NMR (CDCl₃, 400 MHz, ppm): δ 0.85 (t, 6H), 0.99 (t, 6H), 1.15-1.3 (m 8H), 1.45 (pentet, 4H), 2.45-2.6 (6H), 2.66 (t, 1H), 2.79 (dd, 1H), 3.0-3.4 (m, 8H),
20 3.72 (br d, 1H), 3.91 (d, 1H), 4.48 (br s, 1H), 7.0-7.4 (m, 10H)

EXAMPLE 26

25 (S)-2-[(2-(N,N-Diethylamino)ethyl)aminocarbonyl]-4-(N,N-di-n-pentylcarbamoyl)-1-(N,N-diphenylcarbamoyl)-piperazine

According to the procedure of Example 19 above, 40 mg (0.079 mmole) of (S)-1-(N,N-diphenylcarbamoyl)-4-(N,N-di-n-pentylcarbamoyl)piperazine-2-

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carboxylic acid, 12 mg (0.087 mmole) of HOBt, 21 mg (0.11 mmole) of EDAC, and 22 mg (0.16 mmole) of 2-diethylaminoethylamine after purification by flash chromatography on 16 g of silica gel with 100:5:0.2 CH₂Cl₂:MeOH: ammonia water provided 45 mg (93%) of an oil.

Mass Spectrum (FAB): m/Z 607 (M+H, 100%), 438 (10%), 324 (8%), 196 (25%).

¹H NMR (CDCl₃, 400 MHz, ppm): δ 0.85 (t, 6H), 1.02 (t, 6H), 1.15-1.35 (m, 8H), 1.46 (pentet, 4H), 2.5-2.6 (m, 6H), 2.63 (td, 1H), 2.79 (dd, 1H), 3.0-3.4 (m, 9H), 3.75 (br d, 1H), 3.93 (d, 1H), 7.04 (br s, 1H), 7.08-7.2 (m, 6H), 7.28-7.4 (m, 4H).

EXAMPLE 27

(S)-2-[(4-(N,N-Diethylamino)butyl)aminocarbonyl]-1-[N-(3,5-dimethylphenyl)-N-phenylcarbamoyl]-4-(N,N-di-n-pentylcarbamoyl)piperazine

Step A: N-Acetyl-3,5-dimethylaniline

To a solution of 15.2 g (125 mmole) of 3,5-dimethylaniline in 60 mL of toluene was added 15 g (146 mmole) of acetic anhydride, whereupon the internal temperature rose to 75°C. The mixture was allowed to cool to room temperature and the solvent was removed in vacuo. The residue was dissolved in 150 mL of hot ethyl acetate and the solution allowed to stand for 16 hours. The resulting mixture was cooled at 5°C for 3 hours and the solid collected by filtration to give 18.43 g (90%) of off-white crystals.

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¹H NMR (CDCl₃, 400 MHz, ppm): δ 2.14 (s, 3H), 2.29 (s, 6H), 6.73 (s, 1H), 7.05 (br s, 1H), 7.11 (s, 2H).

Step B: N-(3,5-Dimethylphenyl)aniline

5 A mixture of 9.6 g (58.8 mmole) of N-acetyl-3,5-dimethylaniline, 8.13 g (58.8 mmole) of potassium carbonate (dried at 155°C under vacuum), 23 g (147 mmole) of bromobenzene (dried over molecular
10 sieves), and 1.12 g (5.9 mmole) of cuprous iodide was heated in a 175°C oil bath under a reflux condenser under nitrogen for 18 hours. The mixture was cooled to room temperature and triturated with 1 liter of benzene. The solution was concentrated in vacuo. The residue was treated with 60 mL of EtOH and 7.76 g
15 (118 mmole) of potassium hydroxide and the resulting mixture was heated to reflux for two hours. The mixture was cooled and the solvent removed in vacuo. The residue was taken up in 150 mL of hexanes and 20 mL of EtOAc and the resulting solution was washed
20 with 2x100 mL of 2N aqueous HCl and 60 mL of water. The organic layer was dried over sodium sulfate, filtered and concentrated in vacuo. The residue was purified by flash chromatography on 210 g of silica gel with 2 liters of 3:1 hexanes CH₂Cl₂ to give 5.5 g
25 (47%) of a light red oil.
¹H NMR (CDCl₃, 400 MHz, ppm): δ 2.24 (s, 6H), 5.60 (br s, 1H), 5.59 (s, 1H), 6.71 (s, 2H), 6.91 (t, 1H), 7.05 (d, 2H), 7.2-7.3 (m, 2H).

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Step C: N-(3,5-Dimethylphenyl)-N-phenylcarbamoyl chloride

According to the procedure of Example 15, Step A, 5.5 g (27.9 mmole) of N-(3,5-dimethylphenyl)-aniline, 27.9 mL of 1.93 M phosgene in toluene and 15 mL of toluene gave 7.15 g (99%) of a red oil.
¹H NMR (CDCl₃, 400 MHz, ppm): δ 2.29 (s, 6H), 6.92 (br s, 3H), 7.2-7.45 (m, 5H).

Step D: (S)-4-(Benzyloxycarbonyl)-1-[N-(3,5-dimethylphenyl)-N-phenylcarbamoyl]-piperazine-2-carboxylic acid

A mixture of 800 mg (2.72 mmole) of (S)-4-(benzyloxycarbonyl)piperazine-2-carboxylic acid, 707 mg (2.72 mmole) of N-(3,5-dimethylphenyl)-N-phenylcarbamoyl chloride and 760 mg (5.45 mmole) of triethylamine was stirred in 10 mL of DMF for 48 hours at room temperature. The solution was concentrated in vacuo and the residue purified by flash chromatography on 125 g of silica gel eluting with 1 liter of 100:2 CH₂Cl₂:MeOH then 800 mL of 100:5:0.2 CH₂Cl₂:MeOH: HOAc to give 1.32 g of an oil which by ¹H NMR contained residual DMF and HOAc.

Step E: (S)-1-[N-(3,5-Dimethylphenyl)-N-phenylcarbamoyl]-piperazine-2-(S)-carboxylic acid acetate salt

A solution of (S)-1-[N-(3,5-dimethylphenyl)-N-phenylcarbamoyl]-4-(benzyloxycarbonyl) piperazine-2-carboxylic acid (prepared in Step D above) in 9 mL of MeOH was treated with 7 drops of acetic acid

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and 170 mg of 10% Pd/C. The mixture was stirred under an atmosphere of hydrogen for 4 hours, when an additional 50 mg of 10% Pd/C was added. After stirring under an atmosphere of hydrogen for an additional 2 hours, the mixture was filtered through
5 Celite and the filter cake rinsed with 200 mL of MeOH. The filtrate was concentrated in vacuo to give 228 mg of a white paste which was carried on in Step F below.

10 Step F: (S)-1-[N-(3,5-Dimethylphenyl)-N-phenylcarbamoyl]-4-(N,N-di-n-pentylcarbamoyl)-
piperazine-2-carboxylic acid
A mixture of 220 mg (0.53 mmole) of 1-[N-
15 (3,5-dimethylphenyl)-N-phenylcarbamoyl]-piperazine-2-(S)-carboxylic acid acetate salt (from Step E above), 175 mg (0.80 mmole) of N,N-di-n-pentylcarbamoyl
chloride and 188 mg (1.86 mmole) of triethylamine in 6 mL of THF and 3 mL of water was stirred at 55°C for
20 72 hours. To the mixture was added an additional 6 mL of THF, 175 mg of N,N-di-n-pentylcarbamoyl
chloride, and 187 mg of triethylamine and the mixture again heated at 55°C for 48 hours. To the mixture
was added an additional 120 mg N,N-di-n-pentyl-
25 carbamoyl chloride and the reaction mixture heated for an additional 24 hours. The mixture was cooled
and was partitioned between 16 mL of 0.5 N aqueous HCl and 30 mL of EtOAc. The layers were separated
and the aqueous layer extracted with 2x40 mL of
30 EtOAc. The organic layer was dried over magnesium sulfate, filtered and concentrated in vacuo. The

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residue was purified by flash chromatography on 68 g of silica gel eluting with 100:4:0.1 CH₂Cl₂:MeOH:HOAc to give 194 mg (68%) of an oil.

Mass Spectrum (FAB): m/Z 559 (M+Na, 4%), 537 (M+H, 60%), 532 (20%), 492 (M-CO₂H, 5%), 341 (M-PhNAr, 15%), 308 (20%), 224 (ArN(CO)Ph, 95%), 196 (45%), 184 ([CH₃(CH₂)₄]₂NCO, 100%).

¹H NMR (CDCl₃, 400 MHz, ppm): δ 0.85 (t, 6H), 1.1-1.35 (m, 8H), 1.45 (pentet, 4H), 2.24 (s, 6H), 2.64 (t, 1H), 2.90 (d, 1H), 3.05-3.25 (m, 6H), 3.61 (d, 1H), 3.93 (d, 1H), 4.74 (s, 1H), 6.72 (s, 2H), 6.79 (s, 1H), 7.05-7.15 (m, 3H), 7.29 (t, 2H).

Step G: (S)-2-[(4-(N,N-Diethylamino)butyl)amino-carbonyl]-1-[N-(3,5-dimethylphenyl)-N-phenyl-carbamoyl]-4-(N,N-di-n-pentylcarbamoyl)piperazine

According to the procedure of Example 19 above, 40 mg (0.075 mmole) of 1-[N-(3,5-dimethylphenyl)-N-phenylcarbamoyl]-4-(N,N-di-n-pentylcarbamoyl)piperazine-2-carboxylic acid, 12 mg (0.089 mmole) of HOBt, 21 mg (0.112 mmole) of EDAC, and 22 mg (0.15 mmole) of 4-diethylaminobutylamine after purification by flash chromatography on 16 g of silica gel with 100:10:0.2:0.4 CH₂Cl₂:MeOH: ammonia water:water provided 41 mg (84%) of an oil.

Mass Spectrum (FAB): m/Z 663 (M+H, 100%), 466 (M-ArNPh, 3%), 224(ArN(Ph)CO, 25%), 196 (ArNPh, 20%), 184 ([CH₃(CH₂)₄]₂NCO, 18%).

¹H NMR (CDCl₃, 400 MHz, ppm): δ 0.85 (t, 6H), 1.07 (br t, 6H), 1.1-1.3 (m, 8H), 1.4-1.6 (m, 8H), 2.23 (s, 6H), 2.55-2.75 (m, 6H), 2.75 (td, 1H), 2.84 (dd,

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1H), 2.92-3.07 (m, 3H), 3.1-3.35 (m, 5H), 3.68 (d, 1H), 3.93 (d, 1H), 4.47 (s, 1H), 6.72 (s, 2H), 6.79 (s, 1H), 7.08-7.16 (m, 3H), 7.21 (br s, 1H), 7.25-7.33 (m, 2H).

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EXAMPLE 28

(S)-1-[N-(3-Chlorophenyl)-N-phenylcarbamoyl]-2-[(3-(N, N-diethylamino)propyl)aminocarbonyl]-4-(N,N-diphenylcarbamoyl)piperazine

10

According to the procedure of Example 19 above, 20 mg (0.036 mmole) of (S)-1-[N-(3-chlorophenyl)-N-phenylcarbamoyl]-4-(N,N-diphenylcarbamoyl)piperazine-2-carboxylic acid, 6 mg (0.041 mmole) of HOBT, 10 mg (0.051 mmole) of EDAC, and 10 mg (0.072 mmole) of 3-diethylaminopropylamine after purification by flash chromatography on 16 g of silica gel with 100:7:0.2 CH₂Cl₂:MeOH: ammonia water provided 20 mg (83%) of an oil.

Mass Spectrum (FAB): m/Z 667(M+H, 100%), 633 (15%), 230 (25%), 196 (35%).

¹H NMR (CDCl₃, 400 MHz, ppm): δ 1.00 (t, 6H), 1.69 (br pentet, 2H), 2.35-2.65 (m, 7H), 2.86 (dd, 1H), 3.02 (br t, 1H), 3.33 (q, 2H), 3.4-3.55 (m, 2H), 4.22 (d, 1H), 4.42 (br s, 1H), 6.95-7.45 (m, 19H), 7.52 (br s, 1H).

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EXAMPLE 29

(S)-2-[(3-(N,N-Dimethylamino)propyl)aminocarbonyl]-4-(N,N-di-n-pentylcarbamoyl)-1-(N,N-diphenylcarbamoyl)
piperazine

5 According to the procedure of Example 19 above, 40 mg (0.079 mmole) of (S)-1-(N,N-diphenylcarbamoyl)-4-(N,N-di-n-pentylcarbamoyl)piperazine-2-carboxylic acid, 12 mg (0.087 mmole) of HOBt, 21 mg (0.11 mmole) of EDAC, and 20 mg (0.16 mmole) of
10 3-dimethylaminopropylamine after purification by flash chromatography on 16 g of silica gel with 100:7:0.2 CH₂Cl₂:MeOH: ammonia water provided 33 mg (70%) of an oil.

15 Mass Spectrum (FAB): m/Z 593 (M+H, 100%), 196 (15%).
¹H NMR (CDCl₃, 400 MHz, ppm): δ 0.82 (t, 6H), 1.1-1.3 (m, 8H), 1.44 (pentet, 4H), 1.64 (pentet, 2H), 2.20 (s, 6H), 2.25-2.4 (m, 2H), 2.65-2.8 (m, 2H), 3.0-3.35 (m, 8H), 3.73 (d, 1H), 3.88 (d, 1H), 4.47 (br s, 1H),
20 7.05-7.15 (m, 6H), 7.27-7.35 (m, 4H), 7.64 (br t, 1H).

EXAMPLE 30

(S)-2-[(3-(N,N-Diethylamino)propyl)aminocarbonyl]-1-[N-(3,5-dimethylphenyl)-N-phenylcarbamoyl]-4-(N,N-di-n-pentylcarbamoyl)piperazine

25 According to the procedure of Example 19 above, 41 mg (0.076 mmole) of (S)-1-[N-(3,5-dimethylphenyl)-N-phenylcarbamoyl]-4-(N,N-di-n-pentylcarbamoyl)piperazine-2-carboxylic acid, 12 mg (0.092
30 mmole) of HOBt, 22 mg (0.115 mmole) of EDAC, and 21 mg (0.153 mmole) of 4-diethylaminopropylamine after

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purification by flash chromatography on 16 g of silica gel with 100:10:0.3:0.4 CH₂Cl₂:MeOH: ammonia water:water provided 44 mg (88%) of an oil.

Mass Spectrum (FAB): m/Z 649 (M+H, 100%), 224

(ArN(Ph)CO, 25%), 184 ([CH₃(CH₂)₄]₂NCO, 20%).

¹H NMR (CDCl₃, 400 MHz, ppm): δ 0.86 (t, 6H), 0.99 (br s, 6H), 1.15-1.3 (m, 8H), 1.45 (pentet, 4H), 2.23 (s, 6H), 2.4-2.55 (m, 6H), 2.69 (br t, 1H), 2.82 (br d, 1H), 3.0-3.4 (m, 10H), 3.71 (br d, 1H), 3.90 (d, 1H), 4.50 (s, 1H), 6.71 (br s, 2H), 6.78 (s, 1H), 7.05-7.15 (m, 3H), 7.27-7.35 (m, 3H).

EXAMPLE 31

(S)-2-[(2-(N,N-Dimethylamino)ethyl)aminocarbonyl]-4-(N,N-di-n-pentylcarbamoyl)-1-(N,N-diphenylcarbamoyl) piperazine

According to the procedure of Example 19 above, 33 mg (0.065 mmole) of (S)-1-(N,N-diphenylcarbamoyl)-4-(N,N-di-n-pentylcarbamoyl)piperazine-2-carboxylic acid, 10 mg (0.071 mmole) of HOBt, 17 mg (0.091 mmole) of EDAC, and 14 mg (0.13 mmole) of 2-dimethylaminoethylamine after purification by flash chromatography on 16 g of silica gel with 100:7:0.2 CH₂Cl₂:MeOH: ammonia water provided 33 mg (87%) of an oil.

Mass Spectrum (FAB): m/Z 580 (~M+H, 100%), 196 (20%).

¹H NMR (CDCl₃, 400 MHz, ppm): δ 0.85 (t, 6H), 1.12-1.33 (m, 8H), 1.45 (pentet, 4H), 2.22 (s, 6H), 2.39 (t, 2H), 2.67 (td, 1H), 2.81 (dd, 1H), 3.0-3.1 (m, 3H), 3.15-3.40 (m, 5H), 3.72 (d, 1H), 3.94 (d, 1H), 4.53 (s, 1H), 7.06 (br t, 1H), 7.07-7.15 (m, 6H), 7.30 (t, 4H).

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EXAMPLE 32

1,4-bis[N-(3-Chlorophenyl)-N-phenylcarbamoyl]-
2,5-trans-dimethylpiperazine

5 A mixture of 1.33 g (5 mmole) of
3-chlorodiphenylcarbamoyl chloride and 650 mg (5
mmole) of DIEA in 20 mL of methylene chloride was
treated with 286 mg (2.5 mmole) of trans-2,
5-dimethylpiperazine and the mixture was stirred for
10 54 hr. The solution was treated with 20 mL of water,
the layers were separated and the organic layer was
washed with 10 mL each of 2N HCl (twice), 5% aqueous
sodium bicarbonate, water, and saturated sodium
chloride. The organic phase was dried over magnesium
15 sulfate and the solvent was removed in vacuo. The
residue was treated with isopropyl ether to give 712
mg (50%) of a white solid, mp 239-241°C, homogeneous
by TLC (200:1:19 CH₂Cl₂:ammonia water: EtOH).
Mass Spectrum (FAB): m/Z 573(M+H, 100%).

20 Analysis (C₃₂H₃₀N₄O₂Cl₂):

Calculated: C, 67.01; H, 5.27; N, 9.77.

Found: C, 67.07; H, 5.16; N, 9.45.

EXAMPLE 33

25 (S)-4-(Dipentylcarbamoyl)-1-(diphenylcarbamoyl)-2-
(hydroxymethyl)piperazine

1.24 g (2.44 mmole) of (S)-4-(dipentyl-
carbamoyl)-1-(diphenylcarbamoyl)piperazine-2-
30 carboxylic acid dissolved in 6 ml of THF was cooled to
0° in an ice bath. To this 9 ml (9 mmole) of 1.0M

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borane solution in THF was slowly added during a 15 min. period. The resulting mixture was stirred for 24 hr at 25°. The excess hydride was destroyed carefully with 20 ml of a 1:1 mixture of THF and water. The aqueous phase was saturated with anhydrous potassium carbonate. The THF layer was separated and aqueous layer was extracted with ether. The combined organic phase was dried over magnesium sulfate. The solvents were removed on a rotary evaporator to yield 1.18 g (98%) of (S)-4-(dipentyl-carbamoyl)-1-(diphenyl-carbamoyl)-2-(hydroxymethyl) piperazine as a white solid, mp 133-134°.

Mass spectrum (FAB): m/e 495

Analysis (C₂₉H₄₂N₄O₃)

Calculated: C, 70.41; H, 8.56; N, 11.33

Found: C, 70.20; H, 8.68; N, 11.34

EXAMPLE 34

20 Typical Pharmaceutical Compositions Containing a Compound of the Invention

A: Dry Filled Capsules Containing 50 mg of Active Ingredient Per Capsule

25 <u>Ingredient</u>	<u>Amount per capsule (mg)</u>
Active ingredient	50
Lactose	149
Magnesium stearate	<u>1</u>
Capsule (size No. 1)	200

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The active ingredient can be reduced to a No. 60 powder and the lactose and magnesium stearate can then be passed through a No. 60 blotting cloth onto the powder. The combined ingredients can then be mixed for about 10 minutes and filled into a No. 1 dry gelatin capsule.

B: Tablet

A typical tablet would contain the active ingredient (25 mg), pregelatinized starch USP (82 mg), microcrystalline cellulose (82 mg) and magnesium stearate (1 mg).

C: Suppository

Typical suppository formulations for rectal administration contain the active ingredient (0.08-1.0 mg), disodium calcium edetate (0.25-0.5 mg), and polyethylene glycol (775-1600 mg). Other suppository formulations can be made by substituting, for example, butylated hydroxytoluene (0.04-0.08 mg) for the disodium calcium edetate and a hydrogenated vegetable oil (675-1400 mg) such as Suppocire L, Wecobee FS, Wecobee M, Witepsols, and the like, for the polyethylene glycol.

D: Injection

A typical injectible formulation contains the acting ingredient sodium phosphate dibasic anhydrous (11.4 mg), benzyl alcohol (0.01 ml) and water for injection (1.0 ml).

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While the foregoing specification teaches the principles of the present invention, with examples provided for the purpose of illustration, it will be understood that the practice of the invention encompasses all of the casual variations, adaptations, modifications, deletions, or additions of procedures and protocols described herein, as come within the scope of the following claims and its equivalents.

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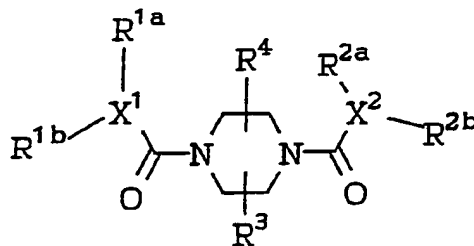
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WHAT IS CLAIMED IS:

1. A compound of structural formula:



I

or a pharmaceutically acceptable salt thereof,
wherein:

R^{1a} is

- 1) H,
 - 2) C₁₋₈ alkyl,
 - 3) phenyl, either unsubstituted or substituted
- with one or two substituents selected from:
- a) -C₁₋₄ alkyl,
 - b) halo,
 - c) -OH,
 - d) -CF₃,
 - e) -NH₂,
 - f) -NH(C₁₋₄ alkyl),
 - g) -N(C₁₋₄ alkyl)₂,
 - h) -CO₂H,
 - i) -CO₂(C₁₋₄ alkyl), and
 - j) -C₁₋₄ alkoxy; or

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4) C₁₋₄ alkyl-phenyl, wherein the phenyl is either unsubstituted or substituted with one or two substituents selected from:

- a) -C₁₋₄ alkyl,
- b) halo,
- c) -OH,
- d) -CF₃
- e) -NH₂,
- f) -NH(C₁₋₄ alkyl),
- g) -N(C₁₋₄ alkyl)₂,
- h) -CO₂H,
- i) -CO₂(C₁₋₄ alkyl), and
- j) -C₁₋₄ alkoxy;

15 R^{1b} is

- 1) R^{1a},
- 2) -C₃₋₇ cycloalkyl, or
- 3) -CH₂-R^{1a};

20 R^{2a} and R^{2b} are independently phenyl, either unsubstituted or substituted with one or two substituents selected from:

- 1) -C₁₋₄ alkoxy,
- 2) halo,
- 3) -OH,
- 4) -CF₃
- 5) -NH₂,
- 6) -NH(C₁₋₄ alkyl),
- 7) -N(C₁₋₄ alkyl)₂,
- 8) -CO₂H,
- 9) -CO₂(C₁₋₄ alkyl), and

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10) -C₁₋₆ alkyl, either unsubstituted or substituted with:

- a) halo,
- b) -OH,
- c) -CF₃,
- d) -NH₂,
- e) -NH(C₁₋₄ alkyl),
- f) -N(C₁₋₄ alkyl)₂,
- g) -CO₂H,
- h) -CO₂(C₁₋₄ alkyl),
- i) C₁₋₄alkoxy,
- j) -S(O)_x(C₁₋₄ alkyl) wherein
x is 0, 1 or 2,
- k) -C₃₋₇ cycloalkyl;

and the phenyl groups of R^{2a} and R^{2b} may be joined together at the ortho carbon atoms through a carbon-carbon single bond or a C₁₋₃ alkylene to form a tricyclic group with the X² to which they are attached;

X¹ is -N, -CH or O, and if X¹ is O, R^{1a} is absent;

X² is -N or -CH;

R³ is

- 1) -C₁₋₄ alkyl,
- 2) -CO₂R⁶,
- 3) -CH₂OCOR⁶,
- 4) -CH₂OH,
- 5) -CH₂OR₅,
- 6) -CH₂S(O)_xR₅,

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- 5 7) $-\text{CH}_2\text{OCONR}^5\text{R}^6$,
 8) $-\text{CH}_2\text{CONR}^5\text{R}^6$,
 9) $-\text{CONR}^5\text{R}^6$,
 10) $-\text{CO}_2\text{R}^8$,
 11) $-\text{CH}_2\text{CO}_2\text{R}^6$,
 12) $-\text{CH}_2\text{CO}_2\text{R}^8$,
 13) $-\text{CONHSO}_2\text{R}^9$,
 14) $-\text{CH}_2\text{N}(\text{R}^6)\text{CONR}^5\text{R}^6$,
 15) $-\text{CH}_2\text{NH}_2$,
10 16) $-\text{CH}_2\text{NH}(\text{C}_{1-4} \text{ alkyl})$, or
 17) $-\text{CH}_2\text{N}(\text{C}_{1-4} \text{ alkyl})_2$; wherein

R^5 is C_{1-6} alkyl either unsubstituted or substituted with:

- 15 1) -halo,
 2) -OH,
 3) $-\text{CF}_3$,
 4) $-\text{NH}_2$,
 5) $-\text{NH}(\text{C}_{1-4} \text{ alkyl})$,
20 6) $-\text{N}(\text{C}_{1-4} \text{ alkyl})_2$,
 7) $-\text{CO}_2\text{H}$,
 8) $-\text{CO}_2(\text{C}_{1-4} \text{ alkyl})$,
 9) $-\text{C}_{3-7}$ cycloalkyl, or
 10) phenyl, either unsubstituted or
25 substituted with
 a) $-\text{C}_{1-4} \text{ alkyl}$,
 b) -halo,
 c) -OH,
 d) $-\text{CF}_3$
30 e) $-\text{NH}_2$,
 f) $-\text{NH}(\text{C}_{1-4} \text{ alkyl})$,
 g) $-\text{N}(\text{C}_{1-4} \text{ alkyl})_2$,

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- h) $-\text{CO}_2\text{H}$, or
 i) $-\text{CO}_2(\text{C}_{1-4} \text{ alkyl})$;

R^6 is $-\text{H}$ or C_{1-4} alkyl; or

5 R^5 and R^6 can be joined together to form with the
 nitrogen to which they are attached $-\text{N}(\text{CH}_2\text{CH}_2)_2\text{L}$,
 wherein L is:

- i) a single bond,
 ii) $-\text{CH}_2-$,
 10 iii) $-\text{O}-$,
 iv) $-\text{S}(0)_p-$, or
 v) $-\text{NR}^7$;

R^7 is

- 15 1) $-\text{H}$,
 2) $-\text{C}_{1-6}$ alkyl, unsubstituted or
 substituted with $-\text{OH}$, $-\text{C}_{1-4}$ alkoxy, or
 $-\text{N}(\text{C}_{1-4}\text{alkyl})_2$,
 3) $-\text{aryl}$, or
 20 4) $-\text{CH}_2-\text{aryl}$;

R^8 is

- 1) $-\text{H}$,
 2) $-\overset{\text{R}^7}{\underset{|}{\text{CH}}}\text{OCOR}^{10}$, wherein R^{10} is
 25 a) $-\text{C}_{1-6}$ alkyl,
 b) $-\text{aryl}$, or
 c) $-\text{CH}_2-\text{aryl}$,
 3) $-\text{CH}_2-\text{aryl}$;

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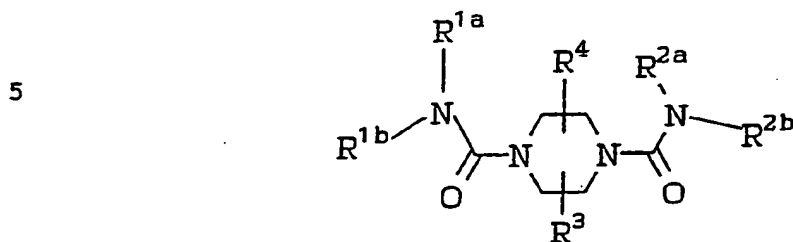
R⁹ is

- 5
- 1) -aryl,
 - 2) -heteroaryl,
 - 3) -C₃₋₇cycloalkyl,
 - 4) -polyfluoro-C₁₋₄alkyl
 - 5) -C₁₋₆alkyl, either unsubstituted or substituted with
- 10
- a) -aryl,
 - b) -heteroaryl,
 - c) -OH,
 - d) -SH,
 - e) -C₁₋₄alkyl,
 - f) -C₃₋₇cycloalkyl,
 - g) -C₁₋₄alkoxy,
 - h) -C₁₋₄alkylthio,
 - 15 i) -CF₃,
 - j) -halo,
 - k) -NO₂,
 - l) -CO₂R⁶,
 - 20 m) -N(R⁶)₂, wherein the R⁶ groups are the same or different,
 - n) -NH aryl,
 - o) -N(aryl)₂,
 - 25 p) -PO₃H,
 - q) -PO(OH)(OC₁₋₄alkyl) or
 - r) -N(CH₂CH₂)₂L, wherein L is as defined above, and

30 R⁴ is H or R³.

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2. The compound of Claim 1 wherein X^1 and X^2 are both N of structural formula:



10 or a pharmaceutically acceptable salt thereof.

3. The compound of Claim 2 wherein:

15 R^{1a} and R^{1b} are independently H, C_{1-8} alkyl or phenyl, either unsubstituted or substituted with -Cl, -Br, -I, -F, C_{1-4} alkyl, or C_{1-4} alkoxy; and R^3 is $-CO_2R^6$, or C_{1-4} alkyl; and

20 R^4 is H or R^3 .

4. The compound of Claim 3 which is selected from the group consisting of:

25

1) 1-(N,N-diphenylcarbamoyl)-4-(N,N-di-n-pentylcarbamoyl)piperazine-2-carboxylic acid;

2) methyl 1-(N,N-diphenylcarbamoyl)-4-(N,N-di-n-pentylcarbamoyl)piperazine-2-carboxylate;

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- 3) 1,4-bis(N,N-diphenylcarbamoyl)piperazine-2-carboxylic acid;
- 5 4) 1,4-bis(N,N-diphenylcarbamoyl)-2-methylpiperazine;
- 5) 1-(N,N-di-n-pentylcarbamoyl)-4-(N,N-diphenylcarbamoyl)piperazine-2-carboxylic acid;
- 10 6) 1-(N-n-pentyl-N-phenylcarbamoyl)-4-(N,N-diphenylcarbamoyl)piperazine-2-carboxylic acid;
- 15 7) 1-[N-(3-chlorophenyl)-N-phenylcarbamoyl]-4-(N,N-di-n-pentylcarbamoyl)piperazine-2-carboxylic acid;
- 8) 1-[N-(3-bromophenyl)-N-phenylcarbamoyl]-4-(N,N-di-n-pentylcarbamoyl)piperazine-2-carboxylic acid;
- 20 9) 1,4-bis(N,N-diphenylcarbamoyl)-~~trans~~-2,5-dimethylpiperazine;
- 25 10) 1,4-bis[N-(3-chlorophenyl)-N-phenylcarbamoyl]-2,5-dimethyl-piperazine; and
- 11) 1,4-bis[N-(3-chlorophenyl)-N-phenylcarbamoyl]-2,5-transdimethylpiperazine;

30 or a pharmaceutically acceptable salt thereof.

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5. The compound of Claim 2 wherein:

5 R^{1a} and R^{1b} are independently H, C₁₋₈ alkyl or
phenyl, either unsubstituted or substituted with
-Cl, -Br, -I, -F, C₁₋₄ alkyl, or C₁₋₄ alkoxy;

10 R³ is -CONR⁵R⁶;
R⁴ is H or R³;
R⁵ is C₁₋₆ alkyl either unsubstituted or substituted
with:

- 10 1) -halo,
 2) -OH,
 3) -CF₃,
 4) -NH₂,
15 5) -NH(C₁₋₄ alkyl),
 6) -N(C₁₋₄ alkyl)₂,
 7) -CO₂H,
 8) -CO₂(C₁₋₄ alkyl),
 9) -C₃₋₇ cycloalkyl, or
20 10) phenyl, either unsubstituted or substituted
with
 a) -C₁₋₄ alkyl,
 b) -halo,
 c) -OH,
25 d) -CF₃,
 e) -NH₂,
 f) -NH(C₁₋₄ alkyl),
 g) -N(C₁₋₄ alkyl)₂,
 h) -CO₂H, or
30 i) -CO₂(C₁₋₄ alkyl); and
R⁶ is -H or C₁₋₄ alkyl.

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6. The compound of Claim 5 which is selected from the group consisting of:

- 5 1) 2-[(2-carboxyethyl)aminocarbonyl]-1-(N,N-diphenylcarbamoyl)-4-(N,N-di-n-pentylcarbamoyl)-piperazine;
- 10 2) 2-[(2-(t-butylcarboxyethyl)aminocarbonyl)-1-(N,N-diphenylcarbamoyl)-4-(N,N-di-n-pentylcarbamoyl)piperazine;
- 15 3) 2-[(3-(N,N-diethylamino)propyl)-N-methylaminocarbonyl]-1-(N,N-diphenylcarbamoyl)-4-(N,N-di-n-pentylcarbamoyl)-piperazine;
- 4) 2-[(2-(N,N-dimethylamino)ethyl)-N-methylaminocarbonyl]-1-(N,N-diphenylcarbamoyl)-4-(N,N-di-n-pentylcarbamoyl)-piperazine;
- 20 5) 2-[(2-(N,N-di(1-methylethyl)amino)ethyl)-aminocarbonyl]-1-(N,N-diphenylcarbamoyl)-4-(N,N-di-n-pentylcarbamoyl)piperazine;
- 25 6) 2-[(3-carboxypropyl)-N-methyl-amino-carbonyl]-1-(N,N-diphenylcarbamoyl)-4-(N,N-di-n-pentylcarbamoyl)piperazine;
- 30 7) 2-[(3-(N,N-diethylamino)propyl)amino-carbonyl]-4-(N,N-di-n-pentylcarbamoyl)-1-(N,N-diphenylcarbamoyl)piperazine;

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- 8) 2-[(4-(N,N-diethylamino)butyl)aminocarbonyl]-
4-(N,N-di-n-pentylcarbamoyl)-1-(N,N-diphenyl-
carbamoyl)piperazine;
- 5 9) 2-[(2-aminoethyl)aminocarbonyl]-4-(N,N-di-
n-pentylcarbamoyl)-1-(N,N-diphenylcarbamoyl)-
piperazine;
- 10 10) 1-[N-(3-chlorophenyl)-N-phenylcarbamoyl]-2-
[(3-(N,N-diethylamino)propyl)aminocarbonyl]-
4-(N,N-di-n-pentylcarbamoyl)piperazine;
- 15 11) 1,4-bis[N-(3-chlorophenyl)-N-phenyl-
carbamoyl]-2-[(3-(N,N-diethylamino)propyl)-
aminocarbonyl]piperazine;
- 20 12) 1-[N-(3-chlorophenyl)-N-phenylcarbamoyl]-2-
[(4-(N,N-diethylamino)butyl)aminocarbonyl]-
4-(N,N-di-n-pentylcarbamoyl)piperazine;
- 25 13) 2-[(3-(N,N-diethylamino)propyl)amino-
carbonyl]-4-(N,N-di-n-pentylcarbamoyl)-1-
[N-(3-methylphenyl)-N-phenylcarbamoyl]-
piperazine;
- 30 14) 1-[N-(3-chlorophenyl)-N-phenylcarbamoyl]-2-
[(2-(N,N-diethylamino)ethyl)aminocarbonyl]-4-
(N,N-di-n-pentylcarbamoyl)piperazine;
- 15) 2-[(2-(N,N-diethylamino)ethyl)aminocarbonyl]-
4-(N,N-di-n-pentylcarbamoyl)-1-(N,N-diphenyl-
carbamoyl)-piperazine;

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- 16) 2-[(4-(N,N-diethylamino)butyl)aminocarbonyl]-
1-[N-(3,5-dimethylphenyl)-N-phenylcarbamoyl]-
4-(N,N-di-n-pentylcarbamoyl)piperazine;
- 5 17) 1-[N-(3-chlorophenyl)-N-phenylcarbamoyl]-2-
[(3-(N,N-diethylamino)propyl)aminocarbonyl]-
4-(N,N-diphenylcarbamoyl)piperazine;
- 10 18) 2-[(3-(N,N-dimethylamino)propyl)amino-
carbonyl]-4-(N,N-di-n-pentylcarbamoyl)-1-
(N,N-diphenylcarbamoyl)piperazine;
- 15 19) 2-[(3-(N,N-diethylamino)propyl)amino-
carbonyl]-1-[N-(3,5-dimethylphenyl)-N-
phenylcarbamoyl]-4-(N,N-di-n-pentyl-
carbamoyl)piperazine;
- 20 20) 2-[(2-(N,N-dimethylamino)ethyl)amino-
carbonyl]-4-(N,N-di-n-pentylcarbamoyl)-1-
(N,N-diphenylcarbamoyl)piperazine;
- 25 21) 2-[(2-(N-methylamino)ethyl-N-methyl-amino-
carbonyl]-4-(N,N-di-n-pentylcarbamoyl)-1-
(N,N-di-n-diphenylcarbamoyl)-piperazine;
- 30 22) 2-[(3-(N,N-diethylamino)propyl)-amino-
carbonyl]-1-[N-(3-methoxy-phenyl)-N-phenyl-
carbamoyl]-4-(N,N-di-n-pentyl-carbamoyl)-
piperazine;

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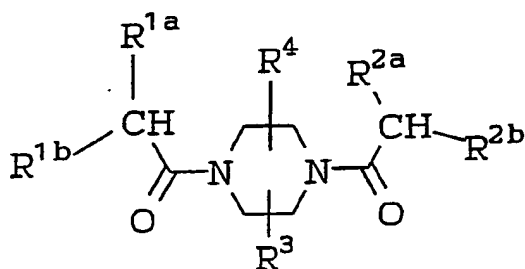
23) 2-[(2-(N,N-diethylamino)ethyl)-N-(2-hydroxyethyl)aminocarbonyl]-4-(N,N-di-n-pentylcarbamoyl)-1-(N,N-diphenylcarbamoyl)-piperazine;

24) 2-[(3-(N,N-diethylamino)propyl)-amino-carbonyl]-1-[N-(4-hydroxyphenyl)-N-phenylcarbamoyl]-4-(N,N-di-n-pentylcarbamoyl)-piperazine; and

25) 2-[(2-(N,N-diethylamino)ethyl)-(N-(2-hydroxy)ethyl)aminocarbonyl]-1-[N-(3-chlorophenyl)-N-phenylcarbamoyl]-4-(N,N-di-n-pentyl-carbamoyl)-piperazine;

or a pharmaceutically acceptable salt thereof.

7. The compound of Claim 1 wherein X^1 and X^2 are both CH of structure:



or a pharmaceutically acceptable salt thereof.

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8. The compound of Claim 7 wherein:

5 R^{1a} and R^{1b} are independently H, C_{1-8} alkyl or
phenyl, either unsubstituted or substituted with
-Cl, -Br, -I, -F, C_{1-4} alkyl, or C_{1-4} alkoxy; and

R^3 is $-CO_2R^6$, or C_{1-4} alkyl; and

R^4 is H or R^3 .

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9. The compound of Claim 8 which is
selected from the group consisting of:

- 15 1) 1-diphenylacetyl-4-(3,4-dimethoxyphenyl-
acetyl)-2-hydroxymethylpiperazine; and
- 2) 1-diphenylacetyl-4-(3,4-dimethoxyphenyl-
acetyl)piperazine-2-carboxylic acid;

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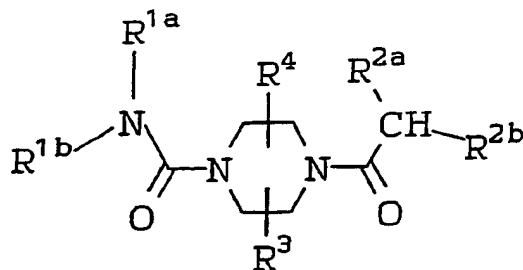
or a pharmaceutically acceptable salt thereof.

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10. The compound of Claim 1 wherein X^1 is N and X^2 is CH of structural formula:



or a pharmaceutically acceptable salt thereof.

11. The compound of Claim 10 wherein:

15 R^{1a} and R^{1b} are independently H, C_{1-8} alkyl or phenyl, either unsubstituted or substituted with -Cl, -Br, -I, -F, C_{1-4} alkyl, or C_{1-4} alkoxy; and

R^3 is $-CO_2R^6$ or C_{1-4} alkyl; and

20 R^4 is H or R^3 .

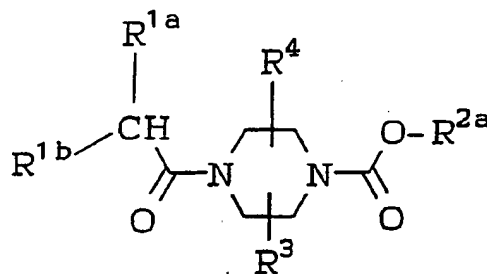
12. The compound of Claim 11 which is selected from the group consisting of:

- 25
- 1) 1-diphenylacetyl-4-(N,N-di-n-pentylcarbamoyl) piperazine-2-carboxylic acid; and
 - 2) methyl 1-diphenylacetyl-4-(N,N-di-n-pentyl-carbamoyl)piperazine-2-carboxylate;
- 30

or a pharmaceutically acceptable salt thereof.

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13. The compound of Claim 1 wherein X^1 is CH and X^2 is O of structural formula:



or pharmaceutically acceptable salt thereof.

14. The compound of Claim 13 wherein:

15 R^{1a} and R^{1b} are independently H, C_{1-8} alkyl or phenyl, either unsubstituted or substituted with -Cl, -Br, -I, -F, C_{1-4} alkyl, or C_{1-4} alkoxy; and

R^3 is $-CO_2R^6$, or C_{1-4} alkyl; and

20

R^4 is H or R^3 .

15. The compound of Claim 14 which is:

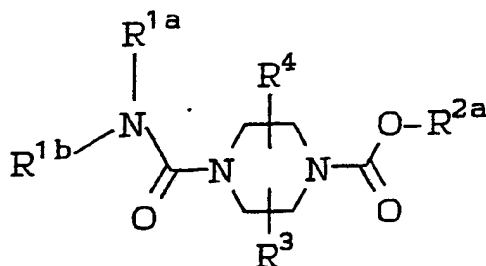
25 1) 1-diphenylacetyl-4-(benzyloxycarbonyl)-piperazine-2-carboxylic acid;

or a pharmaceutically acceptable salt thereof.

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16. The compound of Claim 1 wherein X^1 is N and X^2 is O of structural formula:



or a pharmaceutically acceptable salt thereof.

17. The compound of Claim 16 wherein:

R^{1a} and R^{1b} are independently H, C_{1-8} alkyl or phenyl, either unsubstituted or substituted with -Cl, -Br, -I, -F;

R^{2a} is phenyl, either unsubstituted or substituted with -Cl, Br, -I, F, C_{1-4} alkyl or C_{1-4} alkoxy; and

R^3 is, $-CO_2R^6$, or C_{1-4} alkyl; and

R^4 is H or R^3 .

18. The compound of Claim 17 which is selected from the group consisting of:

- 1) 1-(N,N-diphenylcarbamoyl)-4-(benzyloxy-carbonyl)piperazine-2-carboxylic acid; and

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2) 1-[N-(3-chlorophenyl)-N-phenylcarbamoyl]-4-benzyloxycarbonylpiperazine-2-carboxylic acid;

5 or a pharmaceutically acceptable salt thereof.

19. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and an effective amount of the compound of Claim 1.

20. A method of treating a cerebrovascular, cognitive or central nervous system disorder which is attributed to the binding of angiotensin II to AT₂ receptors in a patient in need thereof which comprises the administration to the patient of an effective amount of the compound of Claim 1.

21. The method of Claim 20 wherein the central nervous system disorder is selected from addiction, anxiety, depression, epilepsy, hyperactivity, pain, Parkinsonism, psychosis, sleep disorders, irregular autonomic function, and tardive dyskinesia.

22. A method for inhibiting the growth of neuronal tumor cells which contain AT₂ receptors in a patient in need thereof which comprises the administration to the patient of an effective amount of the compound of Claim 1.

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23. A method for regulating a reproductive function associated with AT₂ receptors in a female patient in need thereof which comprises the administration to the female patient of an effective amount of the compound of Claim 1.

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24. The method of Claim 23 wherein the reproductive function to be regulated is selected from the menstrual cycle, fertility, and hormonal balances of the estrus cycle.

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25. A method for increasing renal free water clearance in a patient in need thereof which comprises the administration to the patient of an effective amount of the compound of Claim 1.

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26. A method of alleviating the symptoms of premenstrual syndrome associated with retention of water in a female patient in need thereof which comprises the administration to the female patient of an effective amount of the compound of Claim 1.

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27. A method for antagonizing the binding of angiotensin II to dithiothreitol-insensitive receptors in a patient in need thereof which comprises the administration to the patient of an effective amount of the compound of Claim 1.

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28. A method for antagonizing the effect of substance P at its receptor site in a mammal which comprises the administration to the mammal of the compound of Claim 1 in an amount that is effective for antagonizing the effect of substance P at its receptor site in the mammal.

29. A method of treating or preventing a condition selected from the group consisting of: anxiety; colitis; depression or dysthymic disorders; psychosis; allergies; chronic obstructive airways disease; hypersensitivity disorders; vasospastic diseases; fibrosing and collagen diseases; reflex sympathetic dystrophy; addiction disorders; stress related somatic disorders; peripheral neuropathy; neuralgia; neuropathological disorders; disorders related to immune enhancement or suppression; and rheumatic diseases, in a mammal in need of such treatment or prevention which comprises the administration to the mammal of an effective amount of the compound of Claim 1.

30. A method of treating or preventing inflammatory disease in a mammal in need thereof which comprises the administration to the mammal of an effective amount of the compound of Claim 1.

31. A method of treating or preventing pain or migraine in a mammal in need thereof which comprises the administration to the mammal of an effective amount of the compound of Claim 1.

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32. A method of treating or preventing a condition selected from the group consisting of: inflammatory diseases; anxiety; colitis; depression or dysthymic disorders; psychosis; pain; migraine; allergies; chronic obstructive airways disease; hypersensitivity disorders; vasospastic diseases; fibrosing and collagen diseases; reflex sympathetic dystrophy; addiction disorders; stress related somatic disorders; peripheral neuropathy; neuralgia; neuropathological disorders; disorders related to immune enhancement or suppression; and rheumatic diseases, in a mammal in need of such treatment or prevention which comprises the administration to the mammal of an amount of the compound of Claim 1 effective for antagonizing the effect of substance P at its receptor site.

33. A method for the treatment or prevention of cardiovascular diseases and disorders, in a patient in need thereof which comprises the administration to the patient of an effective amount of the compound of Claim 1.

34. A method for the treatment or prevention of coronary insufficiency, hypertension, angina pectoris, cardiac arrhythmia, heart attack, or coronary vasospasm, in a patient in need thereof which comprises the administration to the patient of an effective amount of the compound of Claim 1.

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35. A method for the treatment of multidrug resistant tumor cells comprising the administration to a mammal in need of such treatment of an effective amount of the compound of Claim 1.

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36. A method for the treatment of an insect infestation of an animal host which comprises the administration to such animal host afflicted with such insect infestation of an effective amount of the compound of Claim 1.

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37. A method for the treatment of insect infestations of plants which comprises the administration or application to such plants or the soil in which they grow of an effective amount of the compound of Claim 1.

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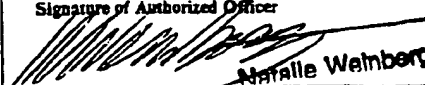
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INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 92/04189

I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all) ⁶		
According to International Patent Classification (IPC) or to both National Classification and IPC Int.Cl.5 C 07 D 241/04 C 07 D 295/20 A 61 K 31/495		
II. FIELDS SEARCHED		
Minimum Documentation Searched ⁷		
Classification System	Classification Symbols	
Int.Cl.5	C 07 D 241/00 C 07 D 295/00	
Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched ⁸		
III. DOCUMENTS CONSIDERED TO BE RELEVANT⁹		
Category ¹⁰	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³
A	EP,A,0343900 (GLAXO) 29 November 1989, see claims ---	1,19
A	Bulletin of the Chemical Society of Japan, vol. 60, no. 9, 1987, (Tokyo, JP), K. SOAI et al.: "Asymmetric sythesis using chiral piperazine. I. Asymmetric synthesis of 2-substituted alcohol and carboxylic acid by diastereoselective alkylation of chiral diamides derived from piperazines", pages 3450-3452, see pages 3450-3452 -----	1
<div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> <p>¹⁰ Special categories of cited documents:</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="width: 45%;"> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"&" document member of the same patent family</p> </div> </div>		
IV. CERTIFICATION		
Date of the Actual Completion of the International Search		Date of Mailing of this International Search Report
18-09-1992		21. 10. 92
International Searching Authority EUROPEAN PATENT OFFICE		Signature of Authorized Officer  Nathalie Weinberg

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 92/04189

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: (Rule 39.1(iv)): Although claims 20-37 are directed to a method of treatment of the human body, the search has been based on the attributed effects of the compounds.
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

SA 60780

For more details about this annex : see Official Journal of the European Patent Office, No. 12/82